NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 451

TOXICOLOGY AND CARCINOGENESIS STUDIES OF NICKEL OXIDE

(CAS NO. 1313-99-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

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July 1996

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CONTENTS

ABSTRACT

NiO

NICKEL OXIDE

CAS No. 1313-99-1

Chemical Formula: NiO Molecular Weight: 74.71

Synonyms: Bunsenite; C.I. 77777; green nickel oxide; mononickel oxide; nickel monoxide; nickel oxide sinter 75; nickel protoxide; nickel (II) oxide; nickel (T+) oxide; nickelous oxide

Nickel oxide (NiO) "sinters" are used in stainless steel and alloy steel production. Nickel oxide was nominated by the National Cancer Institute to the NTP for testing because exposure to this form of nickel is prevalent in the nickel industry. Increased incidences of lung and nasal sinus cancers have occurred among workers in certain nickel refining facilities, and nickel oxide was studied as part of a class study of nickel compounds. Male and female F344/N rats and B6C3F$_1$ mice were exposed to nickel oxide (high temperature, green nickel oxide; mass median diameter 2.2 $\pm$ 2.6 μm; at least 99% pure) by inhalation for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in peripheral blood of B6C3F$_1$ mice exposed to nickel oxide for 13 weeks.

16-DAY STUDY IN RATS

Groups of five male and five female F344/N rats were exposed to 0, 1.2, 2.5, 5, 10, or 30 mg nickel oxide/m^3 (equivalent to 0, 0.9, 2.0, 3.9, 7.9, or 23.6 mg nickel/m^3) by inhalation for 6 hours per day, 5 days per week for a total of 12 exposure days during a 16-day period. Additional groups of five male and five female rats were exposed to 0, 1.2, 5, or 10 mg/m^3 for tissue burden studies. All core study rats survived until the end of the study, final mean body weights of exposed male and female rats were similar to those of the controls, and there were no clinical findings related to nickel oxide exposure. Absolute and relative lung weights of male and female rats exposed to 10 or 30 mg/m^3 were significantly greater than those of the controls. Pigment particles in alveolar macrophages or within the alveolar spaces were observed in the lungs of exposed groups of males and females. Chronic-active inflammation and accumulation of macrophages in alveolar spaces of the lungs and hyperplasia in the respiratory tract lymph nodes were most severe in 10 and 30 mg/m^3 males and females. Hyperplasia of bronchial lymph nodes occurred in 30 mg/m^3 rats. Atrophy of the olfactory epithelium was observed in one male and one female exposed to 30 mg/m^3. The concentrations of nickel oxide in the lungs of exposed groups of rats were greater than those in the lungs of control groups (males, 42 to 267 μg nickel/g lung; females, 54 to 340 μg/g lung).

16-DAY STUDY IN MICE

Groups of five male and five female B6C3F$_1$ mice were exposed to 0, 1.2, 2.5, 5, 10, or 30 mg nickel oxide/m^3 by inhalation for 6 hours per day, 5 days per week for a total of 12 exposure days during a 16-day period. Additional groups of five male and

five female mice were exposed to 0, 1.2, 2.5, or 5 mg/m^3 for tissue burden studies. No exposure-related deaths occurred among core study mice, and final mean body weights of exposed male and female mice were similar to those of the controls. There were no chemical-related clinical findings. Pigment particles were present in the lungs of mice exposed to 2.5 mg/m^3 or greater. Accumulation of macrophages in alveolar spaces was observed in the lungs of 10 and 30 mg/m^3 males and females. The concentrations of nickel oxide in the lungs of exposed groups of mice were significantly greater than those in the lungs of control animals (males, 32 to 84 μg nickel/g lung; females, 31 to 71 μg/g lung).

13-Week Study in Rats

Groups of 10 male and 10 female F344/N rats were exposed to 0, 0.6, 1.2, 2.5, 5, or 10 mg nickel oxide/m^3 (equivalent to 0, 0.4, 0.9, 2.0, 3.9, or 7.9 mg nickel/m^3) by inhalation for 6 hours per day, 5 days per week for 13 weeks. Additional groups of 18 male and 18 female rats were exposed to 0, 0.6, 2.5, or 10 mg/m^3 for tissue burden studies. No exposure-related deaths occurred among core study rats, final mean body weights of exposed male and female rats were similar to those of the controls, and no clinical findings in any group were related to nickel oxide exposure. Lymphocyte, neutrophil, monocyte, and erythrocyte counts; hematocrit values; and hemoglobin and mean cell hemoglobin concentrations in exposed rats were minimally to mildly greater than those of the controls; these differences were most pronounced in females. Mean cell volumes in exposed rats were generally less than those in the controls. Absolute and relative lung weights of exposed groups of males and females were generally significantly greater than those of controls.

Chemical-related nonneoplastic lesions were observed in the lungs of male and female rats exposed to concentrations of 2.5 mg/m^3 or higher, and the severity of these lesions generally increased with exposure concentration. Accumulation of alveolar macrophages, many of which contained black, granular pigment, was generally observed in all exposed groups of males and females, and increased incidences of inflammation occurred in males and females exposed to 2.5 mg/m^3 or higher. In addition, lymphoid hyperplasia and pigment occurred in the bronchial and mediastinal lymph nodes of 2.5, 5, and 10 mg/m^3 males and females.

The concentration of nickel oxide in the lungs of 0.6, 2.5, and 10 mg/m^3 males was greater than in the lungs of controls at 4, 9, and 13 weeks, and nickel continued to accumulate in the lung at the end of the 13-week exposures (4 weeks, 33 to 263 μg nickel/g lung; 9 weeks, 53 to 400 μg/g lung; 13 weeks, 80 to 524 μg/g lung).

13-Week Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to 0, 0.6, 1.2, 2.5, 5, or 10 mg nickel oxide/m^3 by inhalation for 6 hours per day, 5 days per week for 13 weeks. Additional groups of six male and six female mice were exposed to 0, 0.6, 2.5, or 10 mg/m^3 for tissue burden studies. No exposure-related deaths occurred among core study animals, final mean body weights of exposed male and female mice were similar to those of the controls, and no clinical findings in any group were related to nickel oxide exposure. Hematocrit values and erythrocyte counts in 5 and 10 mg/m^3 females were minimally greater than those of the controls, as was the hemoglobin concentration in 5 mg/m^3 females. Absolute and relative lung weights of 10 mg/m^3 males and females were significantly greater than those of controls, and absolute and relative liver weights of 10 mg/m^3 males were significantly less than those of controls.

Accumulation of alveolar macrophages, many of which contained pigment particles, occurred in all groups of mice exposed to nickel oxide. Inflammation (chronic active perivascular infiltrates or granulomatous) occurred in 2.5, 5, and 10 mg/m^3 males and females. In addition, lymphoid hyperplasia and pigment occurred in the bronchial lymph nodes of males and females exposed to 2.5 mg/m^3 or higher.

The concentration of nickel in the lung was greater than that of controls in 0.6, 2.5, and 10 mg/m^3 males at 13 weeks (42 to 736 μg nickel/g lung).

2-YEAR STUDY IN RATS

Survival, Body Weights, Clinical Findings, and Hematology

Groups of 65 male and 65 female F344/N rats were exposed to 0, 0.62, 1.25, or 2.5 mg nickel oxide/m^3 (equivalent to 0, 0.5, 1.0, or 2.0 mg nickel/m^3) by inhalation for 6 hours per day, 5 days per week for 104 weeks. Survival of exposed male and female rats was similar to that of the controls. Mean body weights of 1.25 mg/m^3 females and 2.5 mg/m^3 males and females were slightly lower than those of the controls during the second year of the study. No chemical-related clinical findings were observed in male or female rats during the 2-year study. No chemical-related differences in hematology parameters were observed in male or female rats at the 15-month interim evaluation.

Pathology Findings

Absolute and relative lung weights of 1.25 and 2.5 mg/m^3 males and females were significantly greater than those of the controls at 7 and 15 months. At 2 years, there were exposure-related increased incidences of alveolar/bronchiolar adenomas or alveolar/bronchiolar adenoma or carcinoma (combined) in males and females. Incidences of atypical alveolar epithelial hyperplasia in the lungs generally increased with increasing exposure concentration in male and female rats. Chronic inflammation of the lung was observed in most exposed rats at 7 and 15 months and at 2 years; the incidences in exposed males and females at 2 years were significantly greater than those in the controls, and the severity of the inflammation increased in exposed groups. The incidences of pigmentation in the alveolus of exposed groups of males and females were significantly greater than those of the controls at 7 and 15 months and at 2 years.

Pigmentation in the bronchial lymph nodes similar to that in the lungs was observed in all exposure groups with the exception of 0.62 mg/m^3 males and females at 7 months. Lymphoid hyperplasia was observed in the bronchial lymph nodes of 1.25 and 2.5 mg/m^3 males and females at 7 and 15 months, and the incidence at 2 years generally increased with exposure concentration.

At 2 years, there was an exposure-related increase in the incidence of benign pheochromocytoma in males and females. The incidences of benign pheochromocytoma and adrenal medulla hyperplasia in 2.5 mg/m^3 females and the incidence of benign or malignant pheochromocytoma (combined) in 2.5 mg/m^3 males were significantly greater than those in the controls.

Tissue Burden Analyses

Nickel concentrations in the lung of exposed rats were greater than those in the controls at 7 and 15 months (7 months, 173 to 713 μg nickel/g lung; 15 months, 262 to 1,116 μg/g lung), and nickel concentrations increased with increasing exposure concentration and with time.

2-YEAR STUDY IN MICE

Survival, Body Weights, Clinical Findings, and Hematology

Groups of 74 to 79 B6C3F_1 mice were exposed to 0, 1.25, 2.5, or 5 mg nickel oxide/m^3 by inhalation for 6 hours per day, 5 days per week for 104 weeks. Survival of exposed male and female mice was similar to that of the controls. Mean body weights of 5 mg/m^3 females were slightly lower than those of the controls during the second year of the study. No chemical-related clinical findings were observed in male or female mice during the 2-year study. No chemical-related differences in hematology parameters were observed in male or female mice at the 15-month interim evaluation.

Pathology Findings

At 2 years, the incidence of alveolar/bronchiolar adenoma in 2.5 mg/m^3 females was significantly greater than that of the controls, as was the incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in 1.25 mg/m^3 females. Generally, incidences of chronic inflammation increased with exposure concentration in males and females at 7 and 15 months. Bronchialization of minimal severity in exposed animals and proteinosis were first observed at 15 months. At 2 years, the incidences of chronic inflammation, alveolar epithelial hyperplasia, and proteinosis in exposed groups of males and females were significantly greater than those of the controls. The severity of chronic inflammation increased with exposure concentration in females, and proteinosis was most severe in 5 mg/m^3 males and females. Pigment occurred in the lungs of nearly all exposed

mice at 7 and 15 months and at 2 years, and the severity increased with exposure concentration.

Lymphoid hyperplasia occurred in two animals after 7 months; at 15 months, lymphoid hyperplasia occurred in males exposed to 2.5 and 5 mg/m^3 and in all exposed groups of females. At 2 years, lymphoid hyperplasia occurred in some control animals, but this lesion was still observed more often in exposed males and females and the incidence increased with exposure concentration. Pigmentation was observed in the bronchial lymph nodes of exposed males and females at 7 and 15 months and in nearly all exposed animals at 2 years.

Tissue Burden Analyses

Nickel concentrations in the lungs of exposed mice were greater than those in the controls at 7 and 15 months (7 months, 162 to 1,034 μg nickel/g lung; 15 months, 331 to 2,258 μg/g lung), and nickel concentrations increased with increasing exposure concentration and with time.

GENETIC TOXICOLOGY

No increase in the frequency of micronucleated normochromatic erythrocytes was observed in peripheral blood samples from male or female mice exposed to nickel oxide.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *some evidence of carcinogenic activity** of nickel oxide in male F344/N rats based on increased incidences of alveolar/bronchiolar adenoma or carcinoma (combined) and increased incidences of benign or malignant pheochromocytoma (combined) of the adrenal medulla. There was *some evidence of carcinogenic activity* of nickel oxide in female F344/N rats based on increased incidences of alveolar/bronchiolar adenoma or carcinoma (combined) and increased incidences of benign pheochromocytoma of the adrenal medulla. There was *no evidence of carcinogenic activity* of nickel oxide in male B6C3F$_1$ mice exposed to 1.25, 2.5, or 5 mg/m^3. There was *equivocal evidence of carcinogenic activity* of nickel oxide in female B6C3F$_1$ mice based on marginally increased incidences of alveolar/bronchiolar adenoma in 2.5 mg/m^3 females and of alveolar/bronchiolar adenoma or carcinoma (combined) in 1.25 mg/m^3 females.

Exposure of rats to nickel oxide by inhalation for 2 years resulted in inflammation and pigmentation in the lung, lymphoid hyperplasia and pigmentation in the bronchial lymph nodes, and hyperplasia of the adrenal medulla (females). Exposure of mice to nickel oxide by inhalation for 2 years resulted in bronchialization, proteinosis, inflammation, and pigmentation in the lung and lymphoid hyperplasia and pigmentation in the bronchial lymph nodes.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Nickel Oxide

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Exposure concentrations	0, 0.62, 1.25, or 2.5 mg nickel oxide/m^3 (0, 0.5, 1.0, or 2.0 mg nickel/m^3)	0, 0.62, 1.25, or 2.5 mg nickel oxide/m^3 (0, 0.5, 1.0, or 2.0 mg nickel/m^3)	0, 1.25, 2.5, or 5 mg nickel oxide/m^3 (0, 1.0, 2.0, or 3.9 mg nickel/m^3)	0, 1.25, 2.5, or 5 mg nickel oxide/m^3 (0, 1.0, 2.0, or 3.9 mg nickel/m^3)
Body weights	2.5 mg/m^3 group slightly lower than controls	1.25 and 2.5 mg/m^3 groups slightly lower than controls	Exposed groups similar to controls	5 mg/m^3 group slightly lower than controls
2-Year survival rates	14/54, 15/53, 15/53, 12/52	21/53, 26/53, 20/53, 26/54	19/57, 23/67, 29/66, 23/69	41/64, 40/66, 42/63, 38/64
Nonneoplastic effects	Lung: chronic inflammation (28/54, 53/53, 53/53, 52/52); pigment (1/54, 53/53, 53/53, 52/52) Bronchial lymph node: lymphoid hyperplasia (0/52, 7/51, 10/53, 18/52); pigment (0/52, 45/51, 51/53, 51/52)	Lung: chronic inflammation (18/53, 52/53, 53/53, 54/54); pigment (0/53, 52/53, 53/53, 54/54) Bronchial lymph node: lymphoid hyperplasia (1/49, 5/50, 20/53, 13/52); pigment (0/49, 43/50, 52/53, 47/52) Adrenal medulla: hyperplasia (8/51, 12/52, 14/53, 22/53)	Lung: bronchialization (0/57, 24/67, 40/66, 40/69); proteinosis (0/57, 12/67, 22/66, 43/69); chronic inflammation (0/57, 21/67, 34/66, 55/69); pigment (0/57, 65/67, 66/66, 68/69) Bronchial lymph node: lymphoid hyperplasia (5/45, 18/56, 28/61, 33/62); pigment (0/45, 55/56, 61/61, 60/62)	Lung: bronchialization (0/64, 35/66, 39/63, 40/64); proteinosis (0/64, 8/66, 17/63, 29/64); chronic inflammation (7/64, 43/66, 53/63, 52/64); pigment (0/64, 64/66, 61/63, 64/64) Bronchial lymph node: lymphoid hyperplasia (14/54, 37/63, 40/59, 44/62); pigment (0/54, 58/63, 56/59, 60/62)
Neoplastic effects	Lung: alveolar/bronchiolar adenoma or carcinoma or squamous cell carcinoma (1/54, 1/53, 6/53, 4/52) Adrenal medulla: benign or malignant pheochromocytoma (27/54, 24/52, 27/53, 35/52)	Lung: alveolar/bronchiolar adenoma or carcinoma (1/53, 0/53, 6/53, 5/54) Adrenal medulla: benign pheochromocytoma (4/51, 7/52, 6/53, 18/53)	None	None
Uncertain findings	None	None	None	Lung: alveolar/bronchiolar adenoma (2/64, 4/66, 10/63, 3/64); alveolar/bronchiolar adenoma or carcinoma (6/64, 15/66, 12/63, 8/64)
Level of evidence of carcinogenic activity	Some evidence	Some evidence	No evidence	Equivocal evidence
Genetic toxicology				
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:		Negative in male and female mice		

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

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TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on nickel oxide on November 29, 1994, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On November 29, 1994, the draft Technical Report on the toxicology and carcinogenesis studies of nickel oxide received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, N.C.

Dr. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of nickel oxide by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related nonneoplastic lesions in rats and mice. The proposed conclusions were *some evidence of carcinogenic activity* in male and female F344/N rats, *no evidence of carcinogenic activity* in male B6C3F$_1$ mice, and *equivocal evidence of carcinogenic activity* in female B6C3F$_1$ mice.

Dr. Klaassen, a principal reviewer, agreed with the proposed conclusions. He asked why interim evaluations were conducted at 7 and 15 months. Dr. Dunnick replied that a large database exists for these time points, and they were chosen with the intent to examine the progression of lesions and lung nickel levels. Dr. Klaassen asked why Shirley's test was used for the statistical evaluation of nickel lung burden parameters. Dr. J.K. Haseman, NIEHS, explained that lung burden data are not normally distributed; therefore, a test using rank-based methods (Shirley's test) was considered to be most appropriate.

Dr. Ward, the second principal reviewer, agreed with the proposed conclusions for male and female rats and male mice. But, he suggested a conclusion of *no evidence of carcinogenic activity* for female mice based on the lack of dose response, the absence of any increase in neoplasm multiplicity, and the presence of statistical significance only for alveolar/bronchiolar adenoma or carcinoma (combined) in 1.25 mg/m^3 females. Dr. Ward also noted that although the increase in nickel lung burden measurements was dose related, neoplasm incidence was not. Dr. Haseman said that the lack of a dose response in 5 mg/m^3 females might have been due to significantly increased lung weights, adding that a significant correlation between increased lung weights and decreased lung neoplasm incidence was consistently observed in the three NTP nickel studies. Dr. Ward noted that in the present studies a high incidence of chronic inflammation of the lung was observed in control rats but not in control mice, and he asked if these spontaneous lesions were more specifically focal alveolar macrophages rather than chronic inflammatory lesions resulting from persistent toxins. Dr. M.R. Elwell, NIEHS, said the background inflammatory lesions in control animals were morphologically different from those in exposed animals and were primarily increases in the number of macrophages.

Because Dr. Reddy, the third principal reviewer, was unable to attend the meeting, Dr. L.G. Hart, NIEHS, read his review into the record. Dr. Reddy agreed with the proposed conclusions, although he believed the data for female mice supported a call of *some evidence of carcinogenic activity*. He expressed concern that the highest exposure level selected for rats (2.5 mg/m^3) was too low, and therefore the conclusion of *some evidence* was conservative.

Ms. D. Sivulka, executive director of the Nickel Producers Environmental Research Association, Inc. (NiPERA), commented on the discussion of evidence for nickel toxicity and carcinogenesis in humans and the presentation of the significance of findings relative to existing threshold limit values (TLVs). Ms. Sivulka said that because conclusions in the report were based on existing TLVs, an implication could be made that current regulations are not protective of workers exposed to nickel compounds. Ms. Sivulka discussed the cohorts of workers exposed to nickel compounds that have been examined, and she said that the information obtained from these examinations shows no evidence of nickel-related increases in the incidence of nonneoplastic lesions in workers exposed to low nickel levels.

Dr. Miller noted that TLVs are based to some degree on data obtained from animal studies. Dr. Russo asked if any of the human studies cited by NiPERA had corrected for confounding factors such as alcohol or tobacco exposure. Ms. Sivulka said they had not,

but added that the incidence of neoplasia in workers exposed to nickel compounds could not be attributed solely to factors such as cigarette smoking. Dr. Goldsworthy noted that nickel measurements were generally made without regard to form or species. Ms. Sivulka agreed, but added that NiPERA officials support exposure measurements and speciation analyses. Dr. Miller asked that information interpreting animal studies in terms of likely human exposure be added to the abstract of the Technical Report. Dr. R.A. Griesemer, NIEHS, said the report deals with a specific set of experiments and does not base conclusions on other animal or human studies. Dr. W.T. Allaben, NCTR, noted that the discussion section of the report is the appropriate area to speculate on such issues. He said it was the regulatory agencies' role to determine the significance of the nickel compound studies with regard to human risk.

Dr. Klaassen moved that the Technical Report on nickel oxide be accepted with the revisions discussed and with the conclusions as written for male and female rats, *some evidence of carcinogenic activity*; for male mice, *no evidence of carcinogenic activity*; and for female mice, *equivocal evidence of carcinogenic activity*. Dr. Goldsworthy seconded the motion, which was accepted unanimously with seven votes.

INTRODUCTION

NiO

NICKEL OXIDE

CAS No. 1313-99-1

Chemical Formula: NiO Molecular Weight: 74.71

Synonyms: Bunsenite; C.I. 77777; green nickel oxide; mononickel oxide; nickel monoxide; nickel oxide sinter 75; nickel protoxide; nickel (II) oxide; nickel (T+) oxide; nickelous oxide

CHEMICAL AND PHYSICAL PROPERTIES

Nickel oxide (high temperature green nickel oxide, oxidized at 870°-900° C and heated to 1,350° C; Boldt, 1967) is an olive gray powder with a melting point of 2,090° C and a density of 7.45 g/cm^3. It is insoluble in water and soluble in acids (USEPA, 1986; *Merck Index*, 1989). The mean values for the mass median aerodynamic diameter at each exposure concentration of nickel oxide used in these 2-year studies ranged from 2.2 to 2.6 μm. The nickel oxide used in these studies is only one form of nickel oxide within a larger family of "oxidic" nickels.

PRODUCTION, USE, AND HUMAN EXPOSURE

Nickel was first isolated in 1751 and is found primarily as an oxide (laterite) or sulfide ore (pentlandite) (NIOSH, 1977; Warner, 1984; U.S. Bureau of Mines, 1984, 1985a). In 1991, the six largest nickel producing countries were the Soviet Union, Canada, Australia, New Caledonia, Indonesia, and Cuba. Approximately 55% of the nickel currently used is extracted from sulfide ore, and the remainder is extracted from oxide ore. The total annual world production of nickel is estimated at 1,000,000 tons (900,000 metric tons) (U.S. Bureau of Mines, 1991).

The United States consumption of nickel is approximately 200,000 tons (180,000 metric tons) annually (U.S. Bureau of Mines, 1991). The United States consumes unwrought nickel (68%), ferronickel (17.3%), nickel oxide (11.4%), nickel salts (1.2%), and other forms (2.1%) (U.S. Bureau of Mines, 1984, 1985b). The National Occupational Exposure Survey reported that 56,843 United States workers are potentially exposed to nickel sulfate and 18,165 to nickel oxide (NIOSH, 1991).

Half of the nickel sold each year is used to make stainless steel (Warner, 1984), which contains up to 8% nickel. The ability of nickel to impart corrosion resistance and strength leads to its wide use in chemicals and allied products and in petroleum refining, electrical equipment and supplies, aircraft and parts, construction, fabricated metal products, household appliances, machinery, and ships and boats (U.S. Bureau of Mines, 1984).

Nickel constitutes about 0.008% of the earth's crust. Low levels of nickel are found in air, soil, water, food, and household objects. The average concentration of nickel in finished drinking water is less than 10 ppb. Nickel concentration in United States air has been found to range from 1 to 86 ng/m^3. The most probable nickel species present in the atmosphere include complex nickel, nickel oxide, and nickel sulfate, and the most probable species found in

water include hydrated nickels (ATSDR, 1992). The average amount of nickel in mainstream particulate fractions of cigarette smoke is 79 ng/cigarette (Bache *et al.*, 1985). Dietary intake of nickel per person from foods is estimated at 170 μg per day; intake from inhalation is estimated at 0.1 to 1 μg nickel per day (excluding cigarette smoke), and intake from drinking water is estimated at 2 μg per day (ATSDR, 1992). Nickel is listed as a frequently occurring chemical in waste disposal sites in the United States (*Fed. Regist.*, 1987).

The threshold limit values adopted by the American Conference of Governmental Industrial Hygienists (ACGIH) are 1 mg/m^3 for nickel metal and water-insoluble salts and 0.1 mg/m^3 for water-soluble salts, but the ACGIH published notice of an intended change to 0.05 mg nickel/m^3 for water-soluble and water-insoluble nickel compounds (ACGIH, 1993). The National Institute for Occupational Safety and Health (NIOSH) recommended that the permissible exposure limit for nickel be reduced to 0.015 mg nickel/m^3 averaged over a work shift of up to 10 hours per day, 40 hours per week (NIOSH, 1977).

Atomic absorption spectroscopy is a widely used method for quantifying nickel in the environment and in the workplace. This method of analysis measures total nickel without discerning the forms of nickel present, and most studies of environmental or industrial exposure report total nickel and not the occurrence of individual nickel species (ATSDR, 1992).

ABSORPTION, DISTRIBUTION, AND EXCRETION

Experimental Animals

Animal model systems have been used to obtain information on the absorption, distribution, and excretion of nickel after inhalation exposure (water-soluble and water-insoluble forms of nickel), oral exposure (water-soluble forms of nickel), and dermal exposure (water-soluble forms of nickel).

Intratracheal administration of nickel compounds was one method used by several investigators to study the fate of specific forms of nickel in the lung. English *et al.* (1981) reported on a comparative toxicokinetic study after intratracheal administration of [^{63}Ni]-labeled nickel chloride or nickel oxide (low temperature nickel oxide calcined at 250° C) in Wistar rats. Nickel, after nickel chloride administration, was excreted primarily in the urine. After nickel oxide administration, nickel was equally excreted in the feces and urine. Nickel oxide persisted in the lung for more than 90 days, while nickel chloride was rapidly excreted from the lung with greater than 50% of the nickel cleared from the lungs within 3 days.

Nickel chloride administered as an intratracheal dose to Sprague-Dawley rats was excreted primarily in the urine. By day 3, 90% of the instilled chemical was eliminated from the lungs. The lungs retained 29% of their initial burden at day 1, and this decreased to 0.1% on day 21; 96% of the chemical was excreted in the urine (Carvalho and Ziemer, 1982).

The pulmonary clearance of intratracheally administered nickel subsulfide (Ni_3S_2) in mice has two distinct components with initial and final biological half-lives corresponding to 1.2 and 12.4 days, respectively. The excretion of the chemical (measured as ^{63}Ni) was 60% in the urine and 40% in the feces; 57% of the administered dose was excreted after 3 days with 33% appearing in the urine (Valentine and Fisher, 1984). In another experiment, the calculated clearance times of nickel subsulfide administered intratracheally to mice was also biphasic with a clearance half-life of 2 hours for the first phase and 119 hours for the second phase (Finch *et al.*, 1987).

In F344/N rats administered [^{63}Ni]-labeled nickel oxide (high temperature, green oxide) or nickel subsulfide by pernasal inhalation, the lung half-life was estimated at 120 days for nickel oxide and 5 days for nickel subsulfide (Benson *et al.*, 1994). Following nickel oxide exposure, nickel was not distributed to the extrarespiratory tract tissue, and the material was only excreted in the feces during the first few days after exposure. In contrast, after nickel subsulfide exposure, nickel was detected in extrarespiratory tract tissue including blood and kidney, and nickel was excreted in the urine and the feces. The half-life of [^{63}Ni]-labeled nickel sulfate administered to F344/N rats intratracheally was 1 to 3 days, nickel was present in extrarespiratory tract tissues (including blood, kidney, and intestine), and urine was the major route for excretion of nickel (Medinsky *et al.*, 1987).

Other studies also indicated that nickel oxide has a relatively long half-life in the rodent lung. Nickel

oxide (formed at 550° C; mass median aerodynamic diameter [MMAD] of 0.15 μm, geometric standard deviation [σ_g] of 1.5) given as an aerosol of 750 μg/m^3 to Wistar rats had a bronchial clearance half-life of 1 day and an alveolar clearance half-life of 36 days (Hochrainer *et al.*, 1980). Hochrainer *et al.* (1980) estimated that with continuous exposure to nickel oxide, a steady state would be reached after 1 year.

In Wistar rats after exposure to 0.6 or 8.0 mg nickel oxide/m^3 (high temperature, green oxide; MMAD of 1.2 μm, σ_g of 2.5) for 6 to 7 hours per day for 1 to 2 months, the lung clearance was estimated to be 100 μg per year. There was no apparent deposition of nickel in the liver, kidney, spleen, heart, brain, or blood (Kodama *et al.*, 1985). Lung clearance half-lives for nickel oxide (high temperature, green oxide) in Wistar rats exposed for 1 month were estimated to be 8, 11, and 21 months for nickel oxide with particulate MMADs of 0.6, 1.2, and 4.0 μm, respectively (Tanaka *et al.*, 1985, 1988).

In summary, in absorption and distribution studies for nickel administered intratracheally or by inhalation exposure, the lung half-life was 1 to 3 days for nickel sulfate, 5 days for nickel subsulfide, and greater than 100 days for nickel oxide. Nickel was detected in extrarespiratory tract tissue after exposure to nickel sulfate or nickel subsulfide, but not after exposure to nickel oxide.

The present studies also report findings on the deposition of nickel sulfate hexahydrate, nickel subsulfide, and nickel oxide in the lungs and tissues of rats and mice after 16 days, 13 weeks, and at 7 and 15 months in the 2-year studies. These data show a relatively short half-life in the lung for nickel sulfate hexahydrate, a longer half-life for nickel subsulfide, and the longest half-life for nickel oxide (Benson *et al.*, 1987; Dunnick *et al.*, 1989).

Studies of other routes of nickel exposure in rats, mice, and dogs indicate that 1% to 10% was absorbed after oral administration of nickel sulfate hexahydrate or nickel chloride, and less than 1% of nickel chloride was absorbed through the skin of guinea pigs within 24 hours (ATSDR, 1992; Nielsen *et al.*, 1993).

Humans

In the industrial setting, a major route of nickel exposure in humans is by inhalation (Sunderman, 1992); it is estimated that 35% of inhaled nickel is absorbed into the blood from the respiratory tract (Bennet, 1984; Grandjean, 1984; Sunderman and Oskarsson, 1991). Nickel was excreted in the urine of nickel refinery workers for periods of up to 6 months after facility closing, indicating that there are storage depots in the body that retain nickel for long periods of time (Morgan and Rouge, 1983). There were elevated nickel concentrations in specimens of urine, plasma, and nasal mucosa biopsies obtained from retired workers years after cessation of employment, although the specific form of nickel to which these workers were exposed was not identified (Torjussen and Andersen, 1979; Boysen *et al.*, 1984).

Andersen and Svenes (1989) found elevated levels of nickel in the lungs of nickel refinery workers, although workers who were diagnosed as having lung cancer had the same concentrations of nickel in the lung at autopsy as those who died of other types of cancer. In the workplace setting, exposure to nickel is monitored by analyzing urine, hair, or fingernails for levels of total nickel.

When nickel sulfate was administered to fasting human volunteers, 27% of the administered dose was absorbed when given in drinking water, while only 0.7% was absorbed when administered in food. The elimination half-life for absorbed nickel averaged 28 hours; 100% of the absorbed nickel was eliminated in either the feces or urine within 4 days (Sunderman, 1989, 1992). In studies in humans, reported absorption of radioactive nickel applied to occluded skin varied from 55% to 77% for nickel sulfate to 3% for nickel chloride (ATSDR, 1992).

TOXICITY

Studies of nickel toxicity after experimental or industrial exposure have been summarized in various reviews (NAS, 1975; IARC, 1976, 1984, 1987, 1990; NIOSH, 1977; Brown and Sunderman, 1985; USEPA, 1986; European Chemical Industry, 1989; WHO, 1991; ATSDR, 1992; Nieboer and Nriagu, 1992). In experimental animals and in humans, the primary toxic response to nickel after inhalation occurred in the respiratory system.

Information on the dissolution half-lives for nickel subsulfide and nickel oxide in water and rat serum have been reported. The calculated dissolution half-lives (based on *in vitro* studies) for nickel subsulfide and nickel oxide in water are greater than 7 or 11 years, respectively. In rat serum, the estimated dissolution half-life is 23 days for nickel subsulfide and greater than 11 years for nickel oxide (Sunderman *et al.*, 1987). While nickel subsulfide and nickel oxide are both relatively insoluble in water, nickel subsulfide is more soluble than nickel oxide in biological fluids. Soluble nickel salts (nickel hydroxide) have been shown to be more soluble in human serum than nickel subsulfide (Kasprzak *et al.*, 1983). The comparative toxicity of nickel sulfate hexahydrate, nickel subsulfide, and nickel oxide parallels the solubility of the compounds in biological fluids.

Experimental Animals

The acute toxicity values for selected nickel compounds are summarized in Table 1. Nickel carbonyl [$Ni(CO)_4$] is the most acutely toxic form of nickel, but the use or formation of this nickel compound in manufacturing processes is limited (NAS, 1975). Exposure to nickel oxide, nickel sulfate hexahydrate, or nickel subsulfide is more common in the workplace.

TABLE 1
Toxicity Values for Nickel Carbonyl, Nickel Oxide, Nickel Sulfate Hexahydrate, Nickel Sulfate, and Nickel Subsulfide[a]

Nickel Compound	Species	Route	Toxicity Value[b]
Nickel carbonyl	Rat	Inhalation	35 ppm (LC_{50})
		Subcutaneous	63 mg/kg (LD_{50})
		Intravenous	66 mg/kg (LD_{50})
		Intraperitoneal	39 mg/kg (LD_{50})
	Mouse	Inhalation	67 mg/m^3 (LC_{50})
	Dog	Inhalation	360 ppm (LCLo)
	Cat	Inhalation	1,890 mg/m^3 (LC_{50})
	Rabbit	Inhalation	73 g/m^3 (LCLo)
Nickel oxide	Rat	Subcutaneous	25 mg/kg (LD_{50})
		Intramuscular	180 mg/kg (TDLo)
		Intratracheal	90 mg/kg (TDLo)
	Mouse	Subcutaneous	50 mg/kg (LD_{50})
		Intraperitoneal	400 mg/kg (TDLo)
Nickel sulfate hexahydrate	Dog	Subcutaneous	500 mg/kg (LDLo)
		Intravenous	89 mg/kg (LDLo)
	Cat	Subcutaneous	500 mg/kg (LDLo)
		Intravenous	72 mg/kg (LDLo)
	Rabbit	Subcutaneous	500 mg/kg (LDLo)
		Intravenous	36 mg/kg (LDLo)
	Guinea pig	Subcutaneous	62 mg/kg (LDLo)

(continued)

TABLE 1
Toxicity Values for Nickel Carbonyl, Nickel Oxide, Nickel Sulfate Hexahydrate, Nickel Sulfate, and Nickel Subsulfide (continued)

Nickel Compound	Species	Route	Toxicity Value[b]
Nickel sulfate	Rat	Intraperitoneal	500 mg/kg (LD_{50})
	Mouse	Intraperitoneal	21 mg/kg (LD_{50})
		Intravenous	7 mg/kg (LDLo)
	Dog	Subcutaneous	38 mg/kg (LDLo)
		Intravenous	38 mg/kg (LDLo)
	Cat	Subcutaneous	24 mg/kg (LDLo)
	Rabbit	Subcutaneous	33 mg/kg (LDLo)
		Intravenous	33 mg/kg (LDLo)
Nickel subsulfide	Rat	Inhalation	1 mg/kg (TCLo)
		Subcutaneous	125 mg/kg (TDLo)
		Intravenous	10 mg/kg (TDLo)
		Intramuscular	20 mg/kg (TDLo)
	Mouse	Intramuscular	200 mg/kg (TDLo)

[a] From RTECS (1987)
[b] LC_{50} = median lethal concentration; LCLo = lowest lethal concentration; LD_{50} = median lethal dose; LDLo = lowest lethal dose; TCLo = lowest toxic concentration; TDLo = lowest toxic dose.

In animals, after inhalation exposure to water-soluble and water-insoluble nickel compounds, the primary toxic response is seen in the respiratory system. Changes in a variety of parameters, including dose-related reduction in body weight, reduced leukocyte count, increased urine alkaline phosphatase, and increased erythrocyte count, were observed in Wistar rats continuously exposed to nickel oxide at 200, 400, or 800 $\mu g/m^3$ for 120 days (except for daily cleaning and feeding periods) (Weischer *et al.*, 1980).

Alveolar macrophages from lung lavage fluid from rats exposed to nickel oxide at 120 $\mu g/m^3$ for 12 hours per day, 6 days per week, for 28 days or by intratracheal injection (10 mg nickel oxide/mL) were examined by electron microscopy. Compared to controls, alveolar macrophages from exposed animals were increased in number and enlarged. In the cytoplasm of alveolar macrophages, phagosomes contained osmophilic nickel oxide particles as well as membranous and lamellar structures consistent with accumulation of phospholipid material (Migally *et al.*, 1982; Murthy and Niklowitz, 1983).

Respiratory toxicity to F344/Crl rats administered a single dose of either nickel subsulfide, nickel chloride, nickel sulfate, or nickel oxide by intratracheal instillation was evaluated by examining treatment-related changes in lung lavage fluid (Benson *et al.*, 1986). No significant changes in lung lavage fluid were seen after exposure to nickel oxide. After exposure to nickel subsulfide, nickel sulfate hexahydrate, and nickel chloride, there were increases in the following parameters in lung lavage fluid: lactate dehydrogenase, β-glucuronidase, total protein, glutathione reductase, glutathione peroxidase, and sialic acid. This evaluation was continued by exposing rats or mice to nickel oxide, nickel sulfate hexahydrate, or nickel subsulfide for 13 weeks and looking for treatment-related markers of lung toxicity in lung lavage fluid (Benson *et al.*, 1989). Increases in β-glucuronidase, total protein, neutrophil number, and macrophage number were observed in the lavage fluid after exposure of rats

and mice to all three nickel compounds, although there were quantitative differences in the magnitude of the response. Inflammation was observed histologically in the lung of rats and mice exposed to the three nickel compounds. The severity of lung toxicity as measured by the changes in lung lavage fluid paralleled the severity of histologic changes in the lung. Nickel sulfate hexahydrate was the toxic, and nickel oxide was the least toxic (Benson *et al.*, 1989).

Treatment of rats and mice with water-soluble and water-insoluble nickel salts may cause an alteration of local and systemic immunity, and this toxicity has been studied under various conditions and experiments (Table 2).

TABLE 2
Studies on the Immunologic Effects of Nickel Compounds

Nickel Compound	Species/Route	Treatment	Response	Reference
Cell-Mediated Immunity				
Nickel chloride	CBA/J mice/ intramuscular	Single injection, 18 mg/kg	Reduced T-lymphocyte proliferation	Smialowicz *et al.* (1984)
	Guinea pig	*In vitro* study on spleen cells	Inhibited macrophage migration	Hennighausen and Lange (1980)
Nickel sulfate	B6C3F$_1$ mice (female)/oral	Up to 4,000 mg/kg/day for 23 weeks	Depressed spleen lymphoproliferative response to LPS (no effect on NK activity; PFC assay; mitogen response in spleen cells; resistance to *Listeria* challenge)	Dieter *et al.* (1988)
Nickel subsulfide	Cynomolgus monkey	Intratracheal instillation 0.06 μmol/g lung	No effect on antibody-forming cells (in lung)	Haley *et al.* (1987)
Humoral Immunity				
Nickel chloride	CBA/J mice/ intramuscular	Single injection, 18 mg/kg	Reduced antibody response to T-cell dependent sheep red blood cells	Smialowicz *et al.* (1984)
	C57BL/6J mouse spleen cells	*In vitro* exposure to nickel chloride	Decreased response	Lawrence (1981)
	Swiss albino mice/ intramuscular	3-12 μg Ni/kg body weight followed by immunization with sheep red blood cells	Depressed antibody formation	Graham *et al.* (1975a)
	Swiss mice/ inhalation	2-hour inhalation exposure at 250 μg/m^3	Depressed antibody response to sheep red blood cells	Graham *et al.* (1978)
Nickel acetate	Sprague-Dawley rats/intraperitoneal	11 mg/kg body weight immunized with *E. coli* bacteriophage	Depressed circulating antibody response	Figoni and Treagan (1975)
Nickel oxide	Wistar rats/ inhalation	25-800 μg/m^3 for 4 weeks to 4 months	Decreased ability to form spleen antibodies to sheep red blood cells	Spiegelberg *et al.* (1984)

(continued)

TABLE 2
Studies on the Immunologic Effects of Nickel Compounds (continued)

Nickel Compound	Species/Route	Treatment	Response	Reference
Macrophage Function				
Nickel chloride	CBA/J mice/ intramuscular	Single injection, 18 mg/kg	No effect on phagocytic capacity of peritoneal macrophages	Smialowicz *et al.* (1984)
	Rabbits	Alveolar macrophage *in vitro* exposure	Reduced viability of macrophages	Graham *et al.* (1975b)
Nickel oxide and nickel chloride	Wistar rats/ inhalation	12 hours/day, 6 days/week for 2 weeks at 0.1 mg/m^3	Increased number of alveolar macrophages after nickel oxide; no change after nickel chloride	Bingham *et al.* (1972)
Nickel oxide	Wistar rats/ inhalation	800 μg/m^3 for 2 weeks	Decrease in alveolar macrophage phagocytic ability	Spiegelberg *et al.* (1984)
Nickel subsulfide	Cynomolgus monkey	Intratracheal instillation 0.06 μmol/g lung	Lung macrophage activity decreased	Haley *et al.* (1987)
Natural Killer Cell Activity				
Nickel chloride	CBA/J and C57BL/6J mice/ intramuscular	Single injection, 18 mg/kg	Depressed NK activity (against Yac-1 murine lymphoma cells)	Smialowicz *et al.* (1984, 1985, 1986)
Host Resistance				
Nickel chloride and nickel oxide	CD mice and Sprague-Dawley rats/ inhalation	0.5 mg/m^3 for 2 hours	Enhanced respiratory infection to *Streptococcus*	Adkins *et al.* (1979)

Toxic responses to the immune system were measured in $B6C3F_1$ mice after inhalation exposure to nickel subsulfide, nickel oxide, or nickel sulfate hexahydrate for 6 hours per day and 5 days per week for 13 weeks. Exposure concentrations were 0.11, 0.45, and 1.8 mg nickel/m^3 for nickel subsulfide; 0.47, 2.0, and 7.9 mg nickel/m^3 for nickel oxide; and 0.027, 0.11, and 0.45 mg nickel/m^3 for nickel sulfate hexahydrate. Thymic weights in mice exposed to 1.8 mg nickel/m^3 of nickel subsulfide were lower than those of the controls. Lung-associated lymph nodes were increased in size after exposure to all compounds. The number of alveolar macrophages in lavage samples was increased in mice exposed to the highest concentrations of nickel sulfate hexahydrate and nickel oxide and to 0.45 and 1.8 mg nickel/m^3 nickel subsulfide. Numbers of antibody-forming cells in lung-associated lymph nodes of mice exposed to 2.0 and 7.9 mg nickel/m^3 nickel oxide and 1.8 mg nickel/m^3 nickel subsulfide were greater than those in the controls. Low numbers of antibody-forming cells were observed in the spleens of mice exposed to nickel oxide and in mice exposed to 1.8 mg nickel/m^3 nickel subsulfide. Only mice exposed to 1.8 mg nickel/m^3 nickel subsulfide had a low mixed lymphocyte response. All concentrations of nickel oxide resulted in low levels of alveolar macrophage phagocytic activity, as did 0.45 and 1.8 mg nickel/m^3 nickel subsulfide. None of the nickel compounds affected the phagocytic activity of peritoneal macrophages.

Only 1.8 mg nickel/m^3 nickel subsulfide caused a depressed natural killer cell activity in the spleen. Results indicate that inhalation exposure of mice to nickel can have varying effects on the immune system, depending on dose and physicochemical form of the nickel compound, and these effects were observed at occupationally relevant exposure concentrations (Haley *et al.*, 1990).

Administration of nickel sulfate in the drinking water for 180 days (1 to 10 g/L drinking water, estimated to deliver 116 to 396 mg/kg body weight) resulted in a depressed proliferating response in the bone marrow and spleen of $B6C3F_1$ mice (Dieter *et al.*, 1988).

While experimental studies in animals show the potential of nickel to affect the immune system, the clinical significance of these studies in humans has not been determined (Nicklin and Nielsen, 1992). Further, there are no studies to examine if there is a relationship between effects on the immune system and the carcinogenic effects of nickel.

Humans

Most of the toxicity information on nickel and nickel compounds came from studies of workers in nickel refineries where the primary toxicity is to the respiratory system. In the industrial setting, nickel exposures were occasionally associated with rhinitis, sinusitis, and nasal-septal perforations. Hypersensitive allergic asthmatic reactions to nickel are rare (Nemery, 1990). There were also reports of pulmonary fibrosis in workers inhaling nickel dust (WHO, 1991). While respiratory toxicity has been observed in workers exposed to nickel in the industrial setting, these workers are often exposed to other toxic metals and/or cigarette smoke, and it has not always been possible to conclude that nickel is the sole causative agent of toxicity (ATSDR, 1992). Muir *et al.* (1993) reviewed X-rays of 745 former sinter workers and found no evidence of significant inflammatory or fibrogenic responses in the lungs of the exposed workers.

Nickel contact hypersensitivity has been seen in the general population and in exposed workers. In the general population, contact sensitivity to nickel-containing jewelry and/or prosthesis is another form of nickel toxicity (ATSDR, 1992). Other toxic reactions to nickel were reported in humans in isolated cases where exposures to nickel were not well characterized. These reactions included cardiovascular effects in a child ingesting nickel sulfate and gastrointestinal effects, transient increases in blood reticulocytes, or muscular pain in workers exposed to nickel-contaminated water (ATSDR, 1992). In epidemiologic studies that have shown an association between nickel exposure and cancer, excess mortality from non-malignant respiratory effects or other diseases has not been observed (Doll *et al.*, 1990).

CARCINOGENICITY

Experimental Animals

The International Agency for Research on Cancer (IARC, 1990) summarized the results of experimental studies on the carcinogenic potential of nickel compounds after local injection (e.g., subcutaneous or intramuscular injection). Nickel oxide, nickel subsulfide, nickel carbonyl, and nickel powder cause neoplasms at the injection site, while the soluble nickel salts such as nickel sulfate have generally not been associated with a carcinogenic response at the injection site. A portion of the IARC (1990) listing and tabulation of over 100 experiments on the carcinogenic potential of nickel compounds is presented in Table 3.

Information on the carcinogenic potential of nickel oxide, nickel subsulfide, and nickel sulfate hexahydrate by inhalation exposure is limited. Ottolenghi *et al.* (1975) reported that nickel subsulfide (70% of particles were smaller than 1 μm in diameter; 25% of particles were between 1 and 1.5 μm) caused an increased incidence in lung tumors in F344/N rats exposed to 1 mg/m^3 by inhalation (6 hours/day and 5 days/week for 108 weeks). In the exposed groups, 12% to 14% of the 208 animals examined had lung tumors compared to less than 0.5% of 215 control animals. At the end of the 108-week exposure period, fewer than 5% of the animals in exposed groups were alive compared with a survival of 31% in control groups.

Other experimental studies indicated carcinogenic potential of nickel subsulfide for the respiratory tract mucosa. Yarita and Nettesheim (1978) reported that a single intratracheal dose of 1 or 3 mg nickel subsulfide/kg caused tumors in heterotrophic tracheal transplants in female F344 rats. These authors noted that toxicity might decrease a carcinogenic response resulting in a misleadingly low carcinoma incidence, based on the finding that the more toxic dose (3 mg/kg) caused only a 1.5% incidence of carcinomas (there was a high incidence of tracheal hyperplastic change) versus a 10% carcinoma incidence in the 1 mg/kg group (generally with only a low incidence of toxic lesions).

Hamsters exposed to 53 mg nickel oxide/m^3 (median diameter of 0.3 μm; geometric standard deviation of 2.2) for 2 years did not have an increase in the incidence of lung tumors (Wehner *et al.*, 1975). The hamster may be less sensitive than the rat to the carcinogenic effects of nickel (Furst and Schlauder, 1971).

Sunderman *et al.* (1959) found a low incidence of lung tumors in groups of Wistar rats exposed to nickel carbonyl (0.03 to 0.25 mg/m^3 for 30 minutes 3 times/week for 1 year). Follow-up studies also showed a low incidence of lung tumors in rats exposed to nickel carbonyl (Sunderman and Donnelly, 1965).

Information on the carcinogenic potential of nickel after oral administration is limited (IARC, 1990). Lifetime exposure to nickel acetate at low concentrations (5 ppm) induced no lung lesions in Swiss mice (Schroeder *et al.*, 1964; Schroeder and Mitchener, 1975); the maximum tolerated dose was not reached. Ambrose *et al.* (1976) administered nickel sulfate hexahydrate in the diet of Wistar rats or dogs (0, 100, 1,000, 2,500 ppm) for 2 years, and no treatment-related lesions were observed.

Humans

Exposure to nickel in the workplace has been associated with an increase in lung and nasal sinus tumors (IARC, 1976, 1987, 1990; Doll *et al.*, 1990). Based on the finding of lung and/or nasal sinus tumors in nickel refinery workers, IARC classified nickel and nickel compounds as human carcinogens (Group 1), although there was insufficient information available to evaluate the carcinogenic risk for individual nickel compounds or the risk for cancer based on exposure to different concentrations of nickel compound(s) (IARC, 1987).

Information on the hazards associated with exposure to nickel came from studies on occupational exposure in nickel refineries in Clydach, South Wales; Kristiansand, Norway; the International Nickel Company (INCO) refineries in Ontario, Canada; or from other studies of nickel refineries, nickel mines, or other nickel industrial operations throughout the world (Doll, 1984).

TABLE 3
Summary of Studies Used to Evaluate the Carcinogenicity of Nickel Compounds in Experimental Animals[a]

Nickel Compound	Species/Route	Lesion Incidence[b]	Reference
Nickel oxides and hydroxides			
Nickel monoxide (green)	Rat/inhalation	0.6 mg/m^3: 0/6 lung lesion 8 mg/m^3: 1/8 lung lesion	Horie *et al.* (1985)
Nickel monoxide	Rat/inhalation	0.06 mg/m^3: 0/40 lesion 0.2 mg/m^3: 0/20 lesion	Glaser *et al.* (1986)
	Rat/intrapleural	Controls: 0/32 local lesions 31/32 local lesions	Skaug *et al.* (1985)
	Rat/intratracheal	Controls: 0/40 lesions 10 × 5 mg: 10/37 lung lesions 10 × 15 mg: 12/38 lung lesions	Pott *et al.* (1987)
	Rat/intramuscular	21/32 local lesions	Gilman (1962)
	Rat/intramuscular	2/20 local lesions	Gilman (1966)
	Rat/intramuscular	0/20 local lesions	Sosiński (1975)
	Rat/intramuscular	14/15 local lesions	Sunderman and McCully (1983)
	Rat/intramuscular	0/20 local lesions	Berry *et al.* (1984)
	Rat/subperiosteal	0/20 local lesions	Berry *et al.* (1984)
	Rat/intraperitoneal	46/47 local lesions	Pott *et al.* (1987)
	Rat/intraperitoneal	25 mg: 12/34 local lesions 100 mg: 15/36 local lesions	Pott *et al.* (1989, 1992)
Nickel monoxide (green)	Rat/intrarenal	0/12 local lesions	Sunderman *et al.* (1984)
Nickel monoxide	Mouse/intramuscular	33/50 and 23/52 local lesions	Gilman (1962)
	Hamster/inhalation	1/51 osteosarcoma	Wehner *et al.* (1975, 1979)
	Hamster/intratracheal	Controls: 4/50 lung lesions 1/49 lung lesions	Farrell and Davis (1974)
Nickel hydroxide	Rat/intramuscular	15/20 local lesions	Gilman (1966)
	Rat/intramuscular	Dried gel: 5/19 local lesions Crystalline: 3/20 local lesions Colloidal: 0/13 local lesions	Kasprzak *et al.* (1983)
Nickel trioxide	Rat/intramuscular	0/10 local lesions	Judde *et al.* (1987)
	Rat/intracerebral	3/20 local lesions	Sosiński (1975)

(continued)

TABLE 3
Summary of Studies Used to Evaluate the Carcinogenicity of Nickel Compounds in Experimental Animals (continued)

Nickel Compound	Species/Route	Lesion Incidence	Reference
Nickel sulfides			
Nickel disulfide	Rat/intramuscular	12/14 local lesions	Sunderman (1984)
	Rat/intrarenal	2/10 local lesions	Sunderman *et al.* (1984)
Nickel sulfide (amorphous)	Rat/intramuscular	5.6 mg: 0/10 local lesions 22.4 mg: 0/10 local lesions	Sunderman and Maenza (1976)
ß-Nickel sulfide	Rat/intramuscular	14/14 local lesions	Sunderman (1984)
Nickel sulfide (amorphous)	Rat/intramuscular	3/25 local lesions	Sunderman (1984)
Nickel sulfide	Rat/intrarenal	0/18 local lesions	Jasmin and Riopelle (1976)
ß-Nickel sulfide	Rat/intrarenal	8/14 local lesions	Sunderman *et al.* (1984)
Nickel sulfide (amorphous)	Rat/intrarenal	0/15 local lesions	Sunderman *et al.* (1984)
Nickel subsulfide	Rat/inhalation	14/208 malignant lung lesions 15/208 benign lung lesions	Ottolenghi *et al.* (1975)
	Rat/intratracheal	0.94 mg: 7/47 lung lesions 1.88 mg: 13/45 lung lesions 3.75 mg: 12/40 lung lesions	Pott *et al.* (1987)
	Rat/intrapleural	28/32 local lesions	Skaug *et al.* (1985)
	Rat/subcutaneous	3.3 mg: 37/39 local lesions 10 mg: 37/40 local lesions	Mason (1972)
	Rat/subcutaneous	18/19 local lesions	Shibata *et al.* (1989)
	Rat/intramuscular	25/28 local lesions	Gilman (1962)
	Rat/intramuscular	Controls: 1/19 local lesion 10 mg powder: 19/20 local lesions 10 mg diffusion chamber: 14/17 local lesions 500 mg fragments: 5/7 local lesions 500 mg discs: 14/17 local lesions	Gilman and Herchen (1963)

(continued)

TABLE 3
Summary of Studies Used to Evaluate the Carcinogenicity of Nickel Compounds in Experimental Animals (continued)

Nickel Compound	Species/Route	Lesion Incidence	Reference
Nickel sulfides (continued)			
Nickel subsulfide (disc)	Rat/intramuscular	Removal of disc after 64 days: 4/10 local lesions Removal of disc after 128 days: 7/10 local lesions Removal of disc after 206 days: 10/10 local lesions	Herchen and Gilman (1964)
Nickel subsulfide	Rat/intramuscular	NIH black: 28/28 local lesions Hooded: 14/23 local lesions	Daniel (1966)
	Rat/intramuscular	3.3 mg: 38/39 local lesions 10 mg: 34/40 local lesions	Mason (1972)
	Rat/intramuscular	5 mg: 8/20 local lesions 20 mg: 9/9 local lesions	Sunderman and Maenza (1976)
	Rat/intramuscular	Fischer: 59/63 local lesions Hooded: 11/20 local lesions	Yamashiro *et al.* (1980)
	Rat/intramuscular	0.6 mg: 7/30 local lesions 1.2 mg: 23/30 local lesions 2.5 mg: 28/30 local lesions 5 mg: 29/30 local lesions	Sunderman *et al.* (1976)
	Rat/intramuscular	0.63 mg: 7/29 local lesions 20 mg: 9/9 local lesions	Sunderman (1981)
α-Nickel subsulfide	Rat/intramuscular	9/9 local lesions	Sunderman (1984)
Nickel subsulfide	Rat/intramuscular	10/20 local lesions	Berry *et al.* (1984)
	Rat/intramuscular	2/100 local lesions	Judde *et al.* (1987)
	Rat/intramuscular	19/20 local lesions	Shibata *et al.* (1989)
	Rat/intraperitoneal	9/37 local lesions	Gilman (1966)
	Rat/intraperitoneal	27/42 local lesions	Pott *et al.* (1987)
	Rat/intraperitoneal	6 mg: 20/36 local lesions 12 mg: 25/35 local lesions 25 mg: 25/34 local lesions	Pott *et al.* (1989, 1992)
	Rat/subperiosteal	0/20 local lesions	Berry *et al.* (1984)
	Rat/intrafemoral	10/20 local lesions	Berry *et al.* (1984)
	Rat/intrarenal	In glycerin: 7/16 local lesions In saline: 11/24 local lesions	Jasmin and Riopelle (1976)

(continued)

TABLE 3
Summary of Studies Used to Evaluate the Carcinogenicity of Nickel Compounds in Experimental Animals (continued)

Nickel Compound	Species/Route	Lesion Incidence	Reference
Nickel sulfides (continued)			
α-Nickel subsulfide	Rat/intrarenal	Wistar Lewis: 7/11 local lesions NIH black: 6/12 local lesions Fischer 344: 9/32 local lesions Long-Evans: 0/12 local lesions	Sunderman *et al.* (1979)
Nickel subsulfide	Rat/intratesticular	16/19 local lesions	Damjanov *et al.* (1978)
	Rat/intraocular	14/15 local lesions	Albert *et al.* (1980); Sunderman (1983a)
	Rat/transplacental	No difference in lesion incidence	Sunderman *et al.* (1981)
	Rat/pellet implantation into subcutaneous implanted tracheal grafts	5 mg: 9/60 local lesions 15 mg: 45/64 local lesions	Yarita and Nettesheim (1978)
	Rat/intra-articular	16/19 local lesions	Shibata *et al.* (1989)
	Rat/intra-fat	9/20 local lesions	Shibata *et al.* (1989)
	Mouse/intratracheal	No increase in lung lesion incidence	Fisher *et al.* (1986)
	Mouse/subcutaneous	5 mg: 4/8 local lesions 10 mg: 7/8 local lesions	Oskarsson *et al.* (1979)
	Mouse/intramuscular	Swiss: 27/45 local lesions C3H: 9/18 local lesions	Gilman (1962)
	Mouse/intramuscular	5 mg: 4/8 local lesions 10 mg: 4/8 local lesions	Oskarsson *et al.* (1979)
	Mouse/intramuscular	C57B16: 5/10 local lesions DBA/2: 6/10 local lesions	Sunderman (1983a)
α-Nickel subsulfide	Hamster/intratracheal	0/62 lung lesions	Muhle *et al.* (1992)
Nickel subsulfide	Hamster/intramuscular	Controls: 0/14 local lesions 5 mg: 4/15 local lesions 10 mg: 12/17 local lesions	Sunderman (1983b)
α-Nickel subsulfide	Hamster/topical	54 mg total: 0/6 local lesions 108 mg total: 0/7 local lesions 540 mg total: 0/15 local lesions 1,080 mg total: 0/13 local lesions	Sunderman (1983a)
Nickel subsulfide	Rabbit/intramuscular	16 local lesions	Hildebrand and Biserte (1979a,b)

(continued)

TABLE 3
Summary of Studies Used to Evaluate the Carcinogenicity of Nickel Compounds in Experimental Animals (continued)

Nickel Compound	Species/Route	Lesion Incidence	Reference
Nickel sulfides (continued)			
α-Nickel subsulfide	Rabbit/intramuscular	0/4 local lesions	Sunderman (1983b)
Nickel subsulfide	Salamander/intraocular	7/8 local lesions	Okamoto (1987)
Nickel ferrosulfide	Rat/intramuscular	15/15 local lesions	Sunderman (1984)
	Rat/intrarenal	1/12 local lesions	Sunderman *et al.* (1984)
Nickel salts			
Basic nickel carbonate tetrahydrate	Rat/intraperitoneal	Controls: 1/33 lung lesions 25 mg: 1/35 lung lesions 50 mg: 3/33 lung lesions	Pott *et al.* (1989, 1992)
Nickel acetate	Mouse/intraperitoneal	72 mg: 8/18 lung lesions 180 mg: 7/14 lung lesions 360 mg: 12/19 lung lesions	Stoner *et al.* (1976)
	Rat/intramuscular	1/35 local lesions	Payne (1964)
Nickel acetate tetrahydrate	Mouse/intraperitoneal	Controls: 0.32 lung lesions/animal 1.5 lung lesions/animal	Poirier *et al.* (1984)
	Rat/intraperitoneal	Controls: 1/33 lung lesions 25 mg: 3/35 lung lesions 50 mg: 5/31 lung lesions	Pott *et al.* (1989, 1992)
Nickel ammonium sulfate	Rat/intramuscular	0/35 local lesions	Payne (1964)
Nickel carbonate	Rat/intramuscular	6/35 local lesions	Payne (1964)
Nickel chloride	Rat/intramuscular	0/35 local lesions	Payne (1964)
Nickel chloride hexahydrate	Rat/intraperitoneal	Controls: 1/33 lung lesions 4/32 lung lesions	Pott *et al.* (1989, 1992)
Nickel chromate	Rat/intramuscular	1/16 local lesions	Sunderman (1984)
Nickel fluoride	Rat/intramuscular	3/18 local lesions	Gilman (1966)
Nickel sulfate	Rat/intramuscular	1/35 local lesions	Payne (1964)
	Rat/intramuscular	0/20 local lesions	Gilman (1966)
	Rat/intramuscular	0/20 local lesions	Kasprzak *et al.* (1983)

(continued)

TABLE 3
Summary of Studies Used to Evaluate the Carcinogenicity of Nickel Compounds in Experimental Animals (continued)

Nickel Compound	Species/Route	Lesion Incidence	Reference
Nickel salts (continued)			
Nickel sulfate hexahydrate	Rat/intramuscular	0/32 local lesions	Gilman (1962)
Nickel sulfate heptahydrate	Rat/intraperitoneal	Controls: 1/33 lung lesions 6/30 lung lesions	Pott *et al.* (1989, 1992)
Other			
Nickel carbonyl	Rat/inhalation	30 mg/m^3 for 32 weeks: 1/64 pulmonary lesions 60 mg/m^3 for 32 weeks: 1/32 pulmonary lesions 250 mg/m^3 once: 1/80 pulmonary lesion	Sunderman *et al.* (1957, 1959)
	Rat/inhalation	Controls: 0/32 lung lesions 1/71 lung lesions	Sunderman and Donnelly (1965)
	Rat/intravenous	19/120 lung lesions	Lau *et al.* (1972)

[a] From IARC (1990)
[b] Number of animals with lesion per effective number

The United States Environmental Protection Agency (USEPA, 1986) and the International Committee on Nickel Carcinogenesis in Man (Doll *et al.*, 1990) reviewed the epidemiological evidence for cancer after exposure to nickel in mining or refinery operations. A complete analysis on the type of ore mined and the calcining, smelting, and refining operations in 10 different mines or refineries throughout the world can be found in Doll *et al.* (1990) and in other more recent summaries (Courtin, 1994; McIlveen and Negusante, 1994; Nieboer and Templeton, 1994; Norseth, 1994). Doll *et al.* (1990) also estimate the type of nickel exposures encountered based on knowledge of the nickel process procedures used and a few relatively recent measurements of total airborne nickel. This study focused primarily on "high-risk" cohorts of nickel workers, and many of the workers studied did not have nickel-related cancers.

The first indication that some form of nickel can give rise to lung and nasal sinus cancers was obtained from refinery workers at Clydach, South Wales (Bridge, 1933; Doll, 1958; Morgan, 1958). The Clydach Nickel Refinery (Mond Nickel Works) opened in 1902 and used a nickel-copper matte. In 1933, nasal sinus and lung cancers were first noted in workers who were employed prior to 1925. After 1925, the copper and sulfate content of the matte was reduced, the arsenic contamination in sulfuric acid used to extract copper was reduced, the use of respirators and masks was introduced, and improvements were made in factory design that reduced exposure to nickel (USEPA, 1986; Doll *et al.*, 1990). An increased risk for lung and nasal sinus cancers was particularly noted in refinery work involving roasting, sintering, and calcining processes that converted impure nickel-copper matte to an oxide (Doll *et al.*, 1990).

Peto *et al.* (1984) analyzed the incidence of lung and nasal sinus cancers found in workers in the Clydach plant and found the highest incidence of cancer in

those workers employed in the copper sulfate and furnace areas. There was no increased risk to workers in the reduction area where nickel carbonyl concentrations were highest.

Other evidence for nasal sinus and lung cancer come from studies of workers in the INCO (Ontario, Canada) mines and refineries (Roberts *et al.*, 1989a,b; Muir *et al.*, 1994). Facilities operated include the Sudbury area mines (Copper Cliff Smelter and the Port Colborne refinery) that use an ore that is primarily petlandite ($NiFeS_2$). Men working in mining operations in Ontario had an increase in lung cancer risk, but no nasal sinus cancers (Doll *et al.*, 1990).

The Falconbridge refinery in Kristiansand, Norway, receives nickel-copper matte from Canada and uses an electrolysis process to refine the ore. Workers in roasting and smelting operations are exposed to dry dust containing nickel subsulfide and nickel oxide. Electrolysis workers are also exposed to nickel sulfate and nickel chloride. In this cohort, nasal sinus and lung cancer risks were increased in men working in the electrolysis department, thus implicating the soluble forms of nickel as the cause for the cancer (USEPA, 1986; Doll *et al.*, 1990). The electrolysis workers had the highest average plasma and urine nickel concentrations (Høgetveit *et al.*, 1978).

Enterline and Marsh (1982) studied cancer rates in workers at a refinery in Huntington, West Virginia, which received nickel-copper matte from Canada and/or nickel matte from New Caledonia. The Doll Committee reported no clear evidence for an increased incidence in lung cancer in this population, although the data from this cohort provided weak evidence for an increased incidence in lung cancer in men exposed to sulfidic nickel at 4 mg nickel/m^3 for more than a year (Doll *et al.*, 1990).

Results of epidemiology studies of workers in the nickel mining, smelting, and refinery operations in New Caledonia showed no increased incidence of lung or upper respiratory tract cancers (Goldberg *et al.*, 1994). Nickel at this site is mined from nickel laterites including silicate and limonite ores. The Doll Committee also reported little evidence for an increased incidence in lung or upper respiratory tract cancer in this group of nickel workers (Doll *et al.*, 1990).

The ten cohorts of nickel workers studied by the Doll Committee include the six cohorts mentioned above (nickel refinery operations, Clydach, South Wales; Falconbridge Nickel Mines, Ontario, Canada; INCO mines and refineries [Copper Cliff, Port Colborne, and Coniston], Ontario, Canada; Falconbridge refinery, Kristiansand, Norway; Huntington Alloys, West Virginia; and New Caledonia mines) as well as the Hanna Nickel Smelting Co., Oregon; Oak Ridge Gaseous Diffusion Plant, Tennessee; Outokumpu Oy nickel refinery, Finland; and Henry Wiggin Alloy Co., England (Doll *et al.*, 1990).

The results within the individual cohorts varied, but the overall conclusion by the Doll Committee suggested that more than one form of nickel gives rise to lung and nasal sinus cancer. Much of the respiratory cancer risk was attributed to exposure to a mixture of oxidic and sulfidic nickel. In the absence of sulfidic nickel, exposure to large concentrations of oxidic nickel was also associated with increased lung and nasal sinus cancer risks. There was evidence that exposure to soluble nickel salts increased the risk of lung and nasal sinus cancer and that it may enhance risks associated with exposure to less soluble forms of nickel. There was no evidence that metallic nickel was associated with increased lung and nasal sinus cancer risks. There was no evidence to suggest that exposure to metallic nickel or any of its compounds was likely to produce cancers elsewhere than in the lung or nose. These investigators were not able to provide exposure-specific estimates of risks for individual nickel species. However, the evidence from these studies suggests that respiratory cancer risks in "high-risk" cohorts are primarily related to exposure to water-soluble nickel compounds at concentrations in excess of 1 mg nickel/m^3 and to exposure to less soluble forms at concentrations greater than 10 mg nickel/m^3.

There are no studies evaluating the potential carcinogenic effect in humans specifically after oral exposure to nickel (ATSDR, 1992).

While nickel and nickel compounds are classified by the IARC as Group 1 (human) carcinogens, the mechanism for this carcinogenic activity is not fully understood (Sunderman, 1989; Costa, 1991; Snow, 1992). The mechanisms involved in the induction of cancer by nickel compounds may be related to the ability of nickel ions to interact with chromatin proteins and/or the ability of nickel to generate

intracellular oxidants (Costa *et al.*, 1994). Recent studies suggest that nickel generates free radicals, and the subsequent oxidative reactions lead to DNA damage and cancer. Studies show that 1) incubation of nickel ions with cysteine under aerobic conditions generates hydroxyl radicals and carbon-centered alkyl radicals, suggesting free radicals are generated by nickel (II)-thiol complexes and molecular oxygen (Shi *et al.*, 1993); 2) in forward mutation assays with bacterial DNA, nickel ions produce tandem double CC → TT mutations consistent with damage to DNA by either ultraviolet irradiation or oxygen-free radicals (Tkeshelashvili *et al.*, 1993); and 3) in *in vitro* studies, nickel ions induce increases in 8-hydroxy-2′-deoxyguanosine (8-OH-dG), a biomarker of oxidatively damaged DNA (Littlefield *et al.*, 1991).

After subcutaneous or intramuscular injection of nickel compounds, the water-insoluble nickel compounds are the most potent carcinogens. These findings may be related to the fact that water-insoluble nickel compounds are more readily phagocytized than are the water-soluble nickel salts, which passively diffuse through the cell membrane. Phagocytized nickel particles are internalized in vacuoles whose acidity accelerates the dissolution of nickel ions and results in a higher concentration of nickel than would be achieved by the cellular uptake of water-soluble nickel salts (Costa *et al.*, 1994).

Reproductive and Developmental Toxicity

Experimental Animals

Leonard and Jacquet (1984) reviewed studies which show that water-soluble nickel compounds administered orally or by peritoneal routes have the potential to cause embryotoxicity in rodents. In these studies, the nickel compounds were generally administered at higher doses than humans would be exposed to in drinking water or in the diet.

Studies in rodents have indicated that water-soluble nickel compounds can cross the placenta or be excreted in the milk of lactating animals. When [^{63}Ni]-labeled nickel chloride was administered as an oral bolus dose (10 μmol or 0.58 mg/kg body weight) to pregnant mice, the label was detected in various fetal tissues including liver, kidney, lung, brain, and heart. In another experiment, when [^{63}Ni]-labeled nickel chloride was injected into pregnant mice, nickel was found to cross the placenta, and a marked uptake of nickel was observed in the embryo as measured by whole-body autoradiography (Olsen and Jonsen, 1979). When nickel chloride hexahydrate was given as a single subcutaneous dose (10 to 100 μmol $NiCl_2 \cdot 6H_2O$/kg body weight or 23 mg/kg) to lactating rats, nickel was excreted in the milk and was found in the plasma of the pups (Dostal *et al.*, 1989). The doses used in these studies are higher than the average concentration of nickel found in drinking water in the United States (48 μg/L water) (NAS, 1975).

Nickel chloride administered in the drinking water (50 and 250 ppm, estimated to deliver 7 or 31 mg/kg of nickel compound) to female rats for 11 weeks prior to mating and then during two successive gestation and lactation periods caused an increase in the proportion of dead pups per litter (Smith *et al.*, 1993).

Other studies in rodents administered nickel chloride by intramuscular or intraperitoneal injection during gestation also showed developmental toxicity or fetal death. Nickel chloride injected intraperitoneally (1, 2, or 4 mg/kg body weight) to pregnant Wistar Porton rats on day 8, 12, or 16 of pregnancy caused skeletal retardation (poor ossification), hydrocephalus, hydronephrosis, heart defects, and hemorrhage. At these doses, there was an increase in maternal plasma glucose concentration (Mas *et al.*, 1985).

Nickel chloride injected intramuscularly (16 mg/kg) on day 8 of gestation to Fischer rats reduced the mean number of live pups per dam and diminished fetal body weights on day 20 (Sunderman *et al.*, 1978). Nickel chloride injected into chicken eggs at doses of 0.02 to 0.8 mg per egg on days 0, 1, 2, 3, and 4 after fertilization caused malformations in the embryo including exencephaly, everted viscera, abnormalities in the limb development, microphthalmia, and reduced body size when examined at day 8 (Gilani and Marano, 1980).

Groups of pregnant hamsters were exposed to nickel carbonyl by inhalation (0.06 mg/L for 15 minutes) on days 4, 5, 6, 7, or 8 of gestation; dams were evaluated on day 15 of gestation. Teratogenic effects observed included cystic lung, exencephaly, cleft palate, and fused ribs. In another series of experiments where dams were allowed to deliver the pups,

neonatal mortality was increased in the exposed groups (Sunderman *et al.*, 1980). Nickel carbonyl administered to pregnant dams by intravenous injection (11 mg/kg) on day 7 of gestation caused an increase in fetal mortality, diminished body weight of live pups, and increased incidences of fetal abnormalities including anophthalmia, microphthalmia, cystic lungs, and hydronephrosis (Sunderman *et al.*, 1983).

In a study of nickel oxide, Wistar rats were exposed to 1.6 mg nickel/m^3 by inhalation on gestation days 1 through 20. There was no evidence of embryotoxicity (Weischer *et al.*, 1980).

These and other studies show that water-soluble nickel salts have the potential to cause embryotoxicity in rodents. The metal can cross the feto-maternal barrier and enter the fetus. The embryotoxicity of nickel may be related to several factors including the mutagenic properties of nickel, direct effects on the mammalian embryo, or indirect effects through maternal toxicity. Further work is needed to understand the mechanisms for these effects (Leonard and Jacquet, 1984).

Humans

Until recently, there have been few studies of reproductive effects in humans after exposure to nickel (ATSDR, 1992). A preliminary study of nickel refinery workers in Russia who were exposed to water-soluble nickel salts in electrolysis departments noted a suggested increased risk of pregnancy complications in female workers (Chashschin *et al.*, 1994).

GENETIC TOXICITY

Recent detailed reviews of the mutagenicity of nickel compounds and the possible mechanisms involved in the production of these effects were presented by Coogan *et al.* (1989), Christie and Katisifis (1990), Costa (1991), Snow (1992), and Costa *et al.* (1994). Nickel compounds are not typically detected as bacterial mutagens, but they often give positive results in *in vitro* assays designed to identify compounds that induce chromosomal damage in mammalian cells in the form of sister chromatid exchanges, chromosomal aberrations, and DNA strand breaks. Nickel salts have been shown to inhibit DNA replication and to increase replication errors in mammalian cells *in vitro*, possibly by competing with magnesium for essential binding sites on DNA polymerases (Christie *et al.*, 1991). In addition, positive results were demonstrated in mammalian cell forward mutation assays (TK locus in mouse lymphoma cells and hypoxanthine phosphoribosyl transferase locus in hamster V79 cells), although these responses are usually weak (Nishimura and Umeda, 1979; Amacher and Paillet, 1980; Morita *et al.*, 1991; Lee *et al.*, 1993). Insoluble crystalline nickel compounds are more active in genetic toxicity assays than the soluble or amorphous forms of nickel. Presumably, this differential activity derives from the more efficient entry of insoluble nickels into the cell through phagocytosis (Costa, 1991), longer retention of these compounds within the cell, and the consequent higher intracellular concentration of nickel (II) ions. Soluble nickel salts cannot be efficiently phagocytized and do not accumulate in high concentration within the cell. Based on the results of cell transformation studies in cultured rodent cells, Costa and Heck (1983) concluded that the nickel sulfide compounds must be in the crystalline, rather than in the amorphous state to be efficiently phagocytized into the cell and cause genetic damage. Particle size (Costa and Mollenhauer, 1980) and surface charge (Costa *et al.*, 1982) are also important factors in the phagocytosis of nickel compounds. Insoluble nickel compounds, once inside the cell, aggregate near the nucleus (Bryan, 1981; Evans *et al.*, 1982) where they are dissolved by lysosomes, releasing nickel (II) ions that proceed to effect DNA damage (Costa *et al.*, 1994).

The DNA damage resulting from nickel exposure has been attributed to one or more of the following mechanisms. It may follow the generation of short-lived reactive oxygen species inside the nucleus, produced by the oxidation of Ni^{+2} to Ni^{+3} by hydrogen peroxide or other oxidants subsequent to the binding of nickel ions to ligands such as amino acids, glutathione, and amino acid side chains of nuclear proteins (Biggart and Costa, 1986; Inoue and Kawanishi, 1989; Nieboer *et al.*, 1989; Cotelle *et al.*, 1992; Tkeshelashvili *et al.*, 1993; Sugiyama, 1994). The formation of persistent DNA-protein crosslinks is implicated in the generation of nickel (II)-induced DNA damage (Ciccarelli and Wetterhahn, 1982; Lee *et al.*, 1982; Patierno and Costa, 1985; Sen and Costa, 1986a). Factors involved in the binding of nickel ions to DNA, nuclear proteins, and other nuclear structures are

reviewed by Coogan *et al.* (1989). The binding affinity of nickel to protein is far greater than to purified DNA (Eichorn and Shin, 1968) and therefore, the mutagenic activity of nickel (II) ions probably derives primarily from the binding of nickel to chromosomal protein rather than directly to DNA (Costa, 1991). Nickel binds preferentially to heterochromatic regions of the chromosomes such as the long arm of the X chromosome in cultured Chinese hamster cells (Sen and Costa, 1986a,b; Sen *et al.*, 1987; Costa, 1991); binding of nickel ions to the long arm of the X chromosome and subsequent deletions in this region were postulated to cause the loss of a gene controlling senescence in cultured Chinese hamster cells and to promote immortality in transformed cultured Chinese hamster cell lines (Klein *et al.*, 1991). A schematic representation of some of the proposed mechanisms of nickel-induced genotoxicity, based upon the current understanding of the activities of nickel ions within mammalian cells, is presented in Figure 1. The genetic toxicity data for each of the three nickel compounds under study by the NTP are described below.

The mutagenicity data for nickel oxide are limited; however, there are clear indications of genotoxicity in some *in vitro* test systems. Although exposure to nickel oxide did not result in growth inhibition due to DNA damage in repair-deficient strains of *Bacillus subtilis* (Kanematsu *et al.*, 1980), an S-phase block (determined by flow cytometric analysis) was induced in cycling Chinese hamster ovary cells incubated with 5 μg/mL nickel oxide (Costa *et al.*, 1982). No increase in gene mutations was detected at the ouabain resistance locus in C3H/10$T_{1/2}$ mouse embryo cells (Miura *et al.*, 1989) or at the HPRT locus in hamster V79 cells after exposure to nickel oxide (Kargacin *et al.*, 1993). However, positive effects were reported in mutation assays using a different site, the *gpt* gene, in V79 cells as the target for nickel oxide activity (Kargacin *et al.*, 1993). No induction of chromosomal aberrations was detected in human fibroblast or leukocyte cultures exposed to nickel oxide for 24, 48, or 72 hours (Paton and Allison, 1972); however, the experimental protocol used in this test was designed for water-soluble compounds and may not have been suitable for testing insoluble nickel oxide. Data from human epidemiology studies indicate that exposure to nickel oxide-containing fumes or smelter dusts may induce chromosomal aberrations (Waksvik *et al.*, 1984) and DNA-crosslinks (Costa *et al.*, 1993) in peripheral blood lymphocytes of workers, but the evidence is weak. The link between nickel oxide and these genetic endpoints is confounded because smelter dusts and welding fumes contain other nickel compounds as well as other metals such as chromium and magnesium. Also, the genetic effects noted were not correlated with nickel concentrations in urine or blood, whereas increased DNA-crosslink frequencies noted after exposure to chromium-containing fumes, for example, were correlated with urine concentrations of the metal (Popp *et al.*, 1992).

Nickel sulfate hexahydrate did not induce gene mutations in *Escherichia coli* or *Salmonella typhimurium* (Arlauskas *et al.*, 1985), and (in contrast to results reported for nickel oxide) no increases in *gpt* mutants were observed in hamster V79 cells treated with nickel sulfate hexahydrate (Christie, 1989; Lee *et al.*, 1993). However, nickel sulfate hexahydrate did induce mutations in L5178Y mouse lymphoma $TK^{+/-}$ cells treated with 500 to 1,000 μg/mL in the absence of S9 metabolic activation enzymes (McGregor *et al.*, 1988). In addition, nickel sulfate hexahydrate, administered by injection at doses of 200, 300, and 400 ppm, induced sex-linked recessive lethal mutations in germ cells of male *Drosophila* (Rodriguez-Arnaiz and Ramos, 1986). The pre- and post-meiotic cell stages were affected; the broods obtained from sperm cells undergoing meiosis at the time of treatment showed no evidence of increased lethal mutations. In another test for germ cell effects in male *Drosophila*, the test for sex chromosome loss, only the highest dose of nickel sulfate hexahydrate (400 ppm) resulted in the production of XO males (Rodriguez-Arnaiz and Ramos, 1986). Induction of sister chromatid exchanges and chromosomal aberrations was observed in hamster cells (Larramendy *et al.*, 1981; Ohno *et al.*, 1982), as well as human peripheral lymphocytes (Larramendy *et al.*, 1981) treated with nickel sulfate hexahydrate *in vitro*. However, no induction of DNA single strand breaks was detected in human xeroderma pigmentosum fibroblasts treated with 250 μg/mL nickel sulfate hexahydrate (Fornace, 1982). *In vivo*, no induction of chromosomal aberrations was observed in rat bone marrow or spermatogonial cells after injection of nickel sulfate hexahydrate at doses that provided 3 or 6 mg nickel/kg body weight. Also, no change in the mitotic index of bone marrow cells was noted in treated animals (Mathur *et al.*, 1978).

As with the two nickel compounds discussed above, there are limited published mutagenicity data for the third nickel compound in the present studies, nickel subsulfide. However, results of *in vitro* tests performed with this insoluble nickel compound were mainly positive. In the *Salmonella typhimurium* gene mutation assay, crystalline nickel subsulfide gave equivocal results in one study that used a preincubation protocol (Zeiger *et al.*, 1992) and negative results in a standard plate incorporation assay (Arrouijal *et al.*, 1990). It induced lethal mutations in *Paramecium tetraurelia*, without S9 (Smith-Sonneborn *et al.*, 1986) and unscheduled DNA repair in cultured Syrian hamster embryo cells (Robison *et al.*, 1983). Treatment of cultured Chinese hamster ovary cells for 24 hours with 10 μg/mL nickel subsulfide resulted in an increase in the number of DNA strand breaks detected by alkaline sucrose gradient techniques (Robison *et al.*, 1982). Nickel subsulfide, in the absence of S9, was a weak inducer of hypoxanthine phosphoribosyl transferase mutations in cultured Chinese hamster ovary cells (Rossetto *et al.*, 1994) and sister chromatid exchanges in cultured human lymphocytes (Saxholm *et al.*, 1981). Nickel subsulfide induced significant dose-related increases in chromosomal aberrations (Arrouijal *et al.*, 1990) and micronuclei (Arrouijal *et al.*, 1992) in human lymphocytes *in vitro*. One reported *in vivo* test with nickel subsulfide, a measure of DNA synthesis inhibition in rats administered 10 μg/rat (6 mg/100 g body weight) by intrarenal injection, was negative (Hui and Sunderman, 1980). A second *in vivo* study, a mouse bone marrow micronucleus test, reportedly produced positive results (Arrouijal *et al.*, 1990). This second study, however, employed only a single dose (250 mg/kg nickel subsulfide administered by intraperitoneal injection), and no confirmatory study was conducted.

STUDY RATIONALE

The National Cancer Institute nominated nickel compounds for study because there was little information on the toxic and carcinogenic properties of specific nickel compounds after inhalation exposure. Nickel oxide and nickel sulfate hexahydrate were selected as compounds that are commonly found in the workplace in the United States. Nickel subsulfide was selected for study based on a previous study in which lung tumors were observed in rats (Ottolenghi *et al.*, 1975). The NTP toxicity and carcinogenicity studies of nickel oxide, nickel subsulfide (NTP, 1996a), and nickel sulfate hexahydrate (NTP, 1996b) were performed to provide comparative toxicology and carcinogenicity information on these nickel compounds. The results of the nickel oxide studies are presented in this Technical Report.

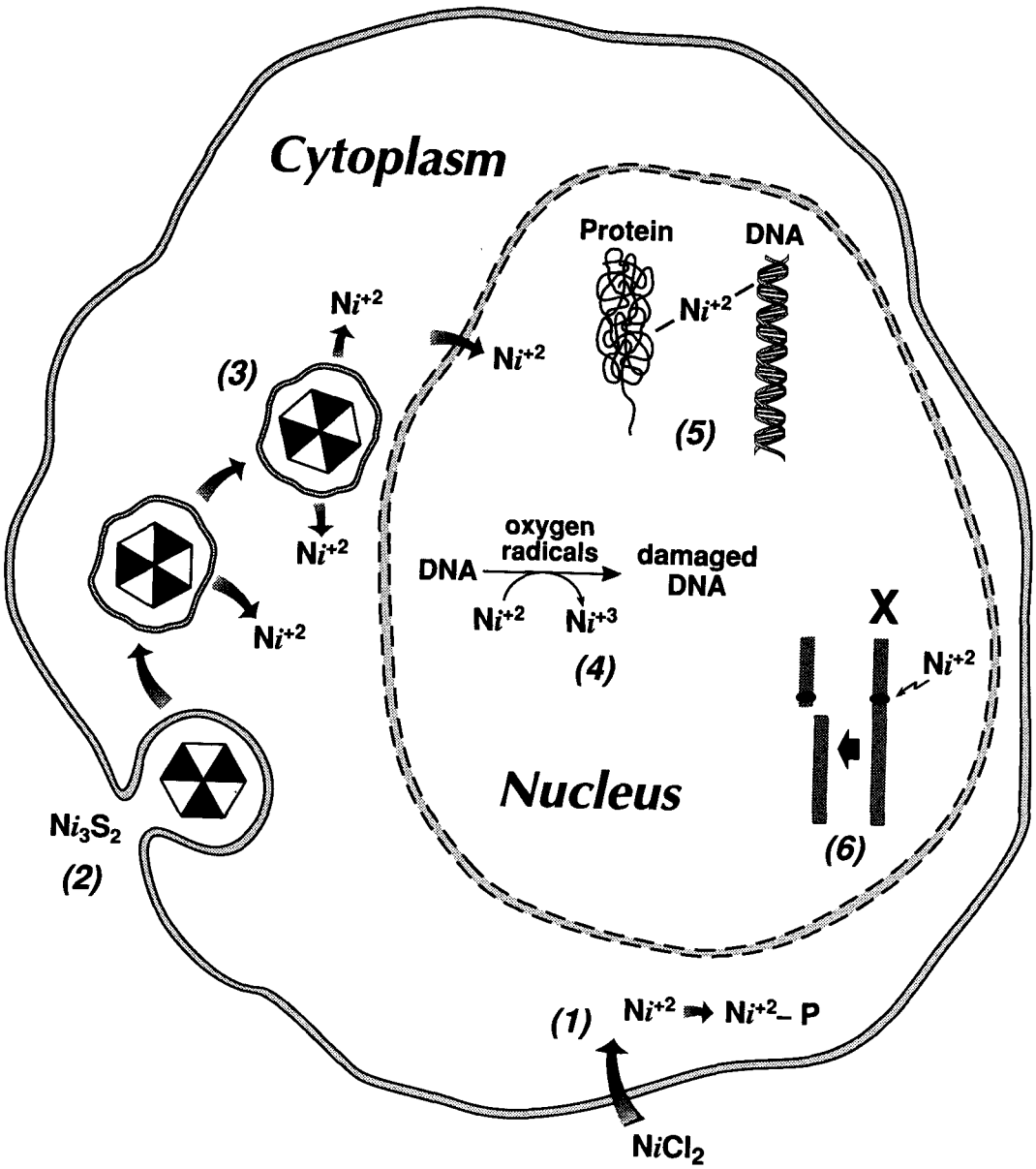

FIGURE 1
Possible Mechanisms of Nickel-Induced Genotoxicity

1. Soluble nickel compounds such as nickel chloride diffuse into the cell; Ni^{+2} ions are rapidly bound to cytoplasmic proteins (P) (Lee *et al.*, 1993). 2. Insoluble nickel compounds such as nickel subsulfide are phagocytized into the cell and move toward the nucleus (Costa *et al.*, 1982). 3. Lysosomal breakdown of insoluble nickel compounds releases large quantities of Ni^{+2} ions which concentrate adjacent to the nuclear membrane (Costa and Heck, 1983). 4. Oxidative damage is induced in DNA by nickel ions bound to nuclear proteins ($Ni^{+2} \rightarrow Ni^{+3}$), releasing active oxygen species (Tkeshelashvili *et al.*, 1993; Sugiyama, 1994). 5. DNA-protein crosslinks are produced by Ni^{+2} ions binding to heterochromatin (Lee *et al.*, 1982; Patierno and Costa, 1985; Sen and Costa, 1986a). 6. Binding of nickel ions to the heterochromatic regions of the long arm of the X chromosome, which may contain a senescence gene and a tumor suppressor gene, can cause deletion of all or part of this region, leading to an immortalization of the cell and clonal expansion (Conway and Costa, 1989; Klein *et al.*, 1991).

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF NICKEL OXIDE

Nickel oxide, which was manufactured by the Societe Metallurgique le Nickel (Paris, France), was generously supplied by International Nickel Company, Ltd. (Toronto, Ontario) in one lot (I042983). Identity and purity analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix K). Reports on analyses performed in support of the nickel oxide studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, an olive gray powder, was characterized as very pure high temperature (sintered) green nickel oxide by elemental analysis, melting point, weight loss on drying, spark source mass spectrometry, and solubility. Elemental analysis for nickel was in agreement with the theoretical value for nickel oxide. The melting point was greater than 300° C. Weight loss on drying indicated less than 0.05% water. Spark source mass spectrometry indicated the major inorganic impurities were cobalt (approximately 2,200 ppm), iron (670 ppm), and sulfur (200 ppm). The sample was not soluble in hot mineral acids, which is expected for sintered nickel oxide. A sample of lot I042983 was analyzed for nickel, cobalt, copper, iron, and sulfur; results indicated conformance with American Society of Testing and Materials specifications for Grade 75 nickel oxide sinter (ASTM, 1974). The overall purity was determined to be greater than 99%.

No accelerated chemical stability studies were performed for nickel oxide based on literature information about the physical and chemical properties of the compound (*Kirk-Othmer*, 1978). The melting point and oxidation state indicate that nickel oxide should be thermally stable at temperatures up to 340° C (Larkins, 1967; Weast, 1976). The bulk chemical was stored in amber glass bottles at room temperature.

Periodic monitoring of the bulk chemical was performed by Huffman Laboratories, Inc., (Golden, CO) using elemental analysis for nickel and weight loss on drying prior to all studies, once during the 16-day and 13-week studies and every 3 to 5 months during the 2-year studies. No change in the purity of the bulk chemical was observed during the studies.

AEROSOL GENERATION AND EXPOSURE SYSTEM

Nickel oxide aerosol was generated from 4-inch (16-day and 13-week studies) or 2-inch (2-year studies) fluid bed generators (FBGs). A Kr-85 discharger was placed in the generator to reduce the electrical charge on the aerosol. The nickel oxide aerosol was mixed with diluting air to achieve the desired concentrations and was delivered to the exposure chambers. The aerosol generation assembly was enclosed in a walk-in hood. Air was circulated through HEPA filters to remove suspended particles in the enclosure. The aerosol delivery system is shown in Figure K2.

Stainless steel, multi-tiered, whole-body exposure chambers (H1000 and H2000, Hazleton Systems, Aberdeen, MD) were used to expose the rats and mice in these studies (Figure K3). The air flow rate was monitored with orifice meters. The air flow rate in the 16-day and 13-week studies corresponded to 3.68 to 21.32 (rats) and 10.06 to 19.44 (mice) air changes per hour. In the 2-year studies, the air flow rate corresponded to 15 $\pm$ 2 air changes per hour. To reduce the spatial variation of aerosol concentration and to increase the uniformity of mixing, the aerosol was diluted in a radial dilutor prior to introduction into the chamber, and a small boxer fan (Model WS 2107FL-1002, Newark Electronics, Chicago, IL) was placed below the aerosol entrance to further mix the aerosol as it entered the chamber.

AEROSOL CONCENTRATION MONITORING

In the 13-week and 2-year studies, the aerosol concentrations were determined gravimetrically from three 2-hour samples (3 L/min flow rate) from each exposure chamber during each 6-hour exposure day. The background concentrations of total suspended particles in the control chambers were monitored each exposure day of the 2-year studies by collecting one 6-hour filter sample. Daily mean exposure concentrations for the 13-week studies are presented in Figures K6 and K7. Weekly mean exposure concentrations for the 2-year studies are presented in Figures K8 and K9. Good control of aerosol concentration was maintained. A continuous aerosol monitor (Model RAM-S, GCA, Co., Bedford, MA) was used to monitor the stability of the aerosol concentrations and to determine the need to adjust the aerosol generation system during exposures. The RAM-S was used to monitor each chamber for at least 2 minutes at the beginning, middle, and end of each filter sampling period.

CHAMBER ATMOSPHERE CHARACTERIZATION

Aerosol size distribution was determined with a cascade impactor once during the 16-day and 13-week studies and monthly during the 2-year studies for each exposure chamber. The particle size was similar for all exposure concentrations and mass median aerodynamic diameters ranged from 1.89 to 3.29 μm with geometric standard deviations ranging from 1.83 to 2.04 (Tables K1 through K4). Prior to the start of the studies, the generated aerosol was sampled and compared to the bulk sample by atomic absorption and X-ray diffraction analyses. The nickel content was identical for both samples, and the diffraction patterns conformed to reference patterns. The data support the conclusion that the crystal structure was not changed during the generation process. Uniformity of aerosol concentration in the exposure chambers was measured prior to the start of the studies without animals in the chambers and with animals during the first week of exposure, and was checked quarterly during the 2-year studies. The spatial variations ranged from 0% to 8.45% for all chambers. The time for the aerosol concentration in the chambers to reach 90% of the target (T_{90}), determined with a RAM-S, was 8 minutes during all studies. The daily exposure time was set at 6 hours plus T_{90}.

16-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from the Frederick Cancer Research Facility (Frederick, MD). On receipt, the rats and mice were approximately 4 weeks old. Animals were quarantined for 19 or 20 days and were approximately 7 weeks old on the first day of exposure. Prior to study start, five male and five female rats and mice were randomly selected for parasite evaluation, gross observation for evidence of disease, and serologic testing.

Groups of five male and five female rats and mice were exposed to nickel oxide by inhalation at concentrations of 0, 1.2, 2.5, 5, 10, or 30 mg nickel oxide/m^3 (equivalent to 0, 0.9, 2.0, 3.9, 7.9, or 23.6 mg nickel/m^3). The animals were exposed for 6 hours plus T_{90} (8 minutes) per day, 5 days per week for 16 days. Feed was available *ad libitum*, except during exposure periods, and water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded initially and on day 5 for rats and mice. The animals were weighed initially, on day 4 or 5, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 4.

In addition, a tissue burden study was performed on five male and five female rats exposed to 0, 1.2, 5, or 10 mg nickel oxide/m^3 and five male and five female mice exposed to 0, 1.2, 2.5, or 5 mg nickel oxide/m^3. The extent of distribution of inhaled nickel was determined in the right kidney and lung of rats and in the lung of mice (Table 4). Rats and mice were anesthetized with halothane and killed by cardiac puncture the morning following the last exposure. Tissue samples were digested with a mixture of nitric and hydrochloric acids and hydrogen peroxide and heated in a microwave oven. The digestates were diluted with deionized water (Millipore Co., Bedford, MA), and the nickel content was determined using electrothermal atomic absorption spectroscopy. Limits of detection and quantitation of the analytical method were calculated on a cumulative basis for each set of samples analyzed

according to a formula given by Keith *et al.* (1983). The results of tissue burden studies in the lung and kidney of rats and lung of mice are presented in Appendixes H and I.

A necropsy was performed on all animals. The brain, heart, right kidney, liver, lung, right testis, and thymus of animals surviving until the end of the study were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed, trimmed, embedded in paraffin, sectioned to a thickness of 5 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all 0 and 30 mg/m^3 rats and mice and on selected organs from rats and mice in all other exposure groups. Table 4 lists the tissues and organs that were examined.

13-WEEK STUDIES

These studies were conducted to evaluate the cumulative toxic effects of repeated inhalation exposure to nickel oxide and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA). Upon receipt, the rats and mice were approximately 4 weeks old. Animals were quarantined for 19 or 20 days and were approximately 7 weeks old on the first day of exposure. Prior to study start, five male and five female rats and mice were randomly selected for parasite evaluation, gross observation for evidence of disease, and serologic testing. At the end of the studies, serologic analyses were performed on groups of five male and five female control animals using the protocols of the NTP Sentinel Animal Program (Appendix M).

Groups of 10 male and 10 female rats and mice were exposed to nickel oxide by inhalation at concentrations of 0, 0.6, 1.2, 2.5, 5, or 10 mg nickel oxide/m^3 (equivalent to 0, 0.4, 0.9, 2.0, 3.9, or 7.9 mg nickel/m^3). The animals were exposed for 6 hours plus T_{90} (8 minutes) per day, 5 days per week for 13 weeks (excluding one holiday). Feed was available *ad libitum*, except during exposure periods and water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded prior to the start of the study and then weekly for rats and mice. The animals were weighed initially, weekly thereafter, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 4.

Tissue burden studies were performed to quantitate the extent of distribution of inhaled nickel in 18 male and 18 female rats and in six male and six female mice exposed to 0, 0.6, 2.5, or 10 mg/m^3. The lungs of six male and six female rats in each group after 4, 9, and 13 weeks and of all mice after 13 weeks were analyzed using the same methods described for the 16-day studies (Table 4). Results of tissue burden studies in the lung of male rats and male mice are given in Appendixes H and I.

At the end of the 13-week studies, samples were collected from core study rats and mice exposed to 0, 2.5, 5, or 10 mg/m^3 for sperm morphology and vaginal cytology evaluations. The parameters evaluated are listed in Table 4. Methods used were those described in the NTP General Statement of Work (April, 1987). For 7 consecutive days prior to the end of the studies, the vaginal vaults of the females were moistened with saline, if necessary, and aspirated samples of vaginal fluid and cells were transferred to slides, air dried, fixed, and stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined to ascertain estrous cycle stage (i.e., estrus, metestrus, diestrus, or proestrus). Male rats and mice were evaluated for sperm morphology, count, and motility. The right testis and epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted by two observers in five fields per slide. Following completion of sperm motility estimates, the cauda epididymis was placed in buffered saline solution and finely minced; the tissue was incubated in the saline solution and heat fixed at 65° C. Sperm density was then determined microscopically using a hemocytometer. To quantify

spermatogenesis, testicular spermatid head count was determined in the left testis by removing the tunica albuginea and homogenizing the testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Results of reproductive tissue evaluations and estrous cycle characterization are given in Appendix J.

At the end of 13 weeks, hematology studies were performed on all surviving rats and mice. The animals were anesthetized with halothane and blood was collected by cardiac puncture and placed in tubes containing heparin as the anticoagulant. Hematology determinations were performed on a Coulter Electronics model S-550 hematology analyzer (Coulter Electronics, Hialeah, FL). Leukocyte differential and nucleated erythrocyte counts were determined by light microscopic examination of blood films stained with Wright-Giemsa. Reticulocyte counts were determined by light microscopy, using smears stained with new methylene blue. The hematology parameters measured are listed in Table 4.

A necropsy was performed on all animals. The brain, heart, right kidney, liver, lung, right testis, and thymus of animals surviving until the end of the study were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed, trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all 0 and 10 mg/m^3 rats and mice, and on selected organs from rats and mice in the other exposure groups. Table 4 lists the tissues and organs that were examined.

2-YEAR STUDIES

Study Design

Groups of 65 male and 65 female rats were exposed to nickel oxide by inhalation at concentrations of 0, 0.62, 1.25, or 2.5 mg nickel oxide/m^3 (equivalent to 0, 0.5, 1.0, or 2.0 mg nickel/m^3) and groups of as many as 79 male and 76 female mice were exposed to nickel oxide by inhalation at concentrations of 0, 1.25, 2.5, or 5 mg nickel oxide/m^3 (equivalent to 0, 1.0, 2.0, or 3.9 mg nickel/m^3) for 6 hours plus T_{90} (8 minutes) per day, 5 days per week for 104 weeks, excluding holidays. After 7 months of exposure, as many as seven male and seven female rats and five male and five female mice from each exposure group were evaluated for histopathology and tissue burden. After 15 months of exposure, five male and five female rats and mice were evaluated for hematology parameters, histopathology, and tissue burden.

Source and Specification of Animals

Male and female F344/N rats were obtained from Taconic Farms (Germantown, NY) and male and female B6C3F$_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA) for use in the 2-year studies. Upon receipt the animals were 4 weeks old. Animals were quarantined for 11 days before the beginning of the studies and were approximately 6 weeks old on the first day of exposure. Prior to study start, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix M).

Animal Maintenance

Rats and mice were housed individually. Feed was available *ad libitum*, except during exposure periods, and water was available *ad libitum*. Cages and racks were rotated weekly. Further details of animal maintenance are given in Table 4. Information on feed composition and contaminants is provided in Appendix L.

Clinical Examinations and Pathology

The animals were observed twice daily for signs of toxicity, mortality, or moribundity. Clinical findings and body weights were recorded initially, weekly for the first 13 weeks, monthly thereafter, and at the end of the studies.

At 15 months, rats and mice were anesthetized with carbon dioxide and blood was drawn from the retroorbital sinus and placed in tubes containing potassium EDTA as the anticoagulant. The hematology parameters measured are listed in Table 4.

Lung samples for determination of tissue burden were collected from rats exposed to 0, 0.62, 1.25, or 2.5 mg/m^3 and from mice exposed to 0, 1.25, 2.5, or 5 mg/m^3 after 7 and 15 months and were analyzed using the same methods used in the 16-day studies.

The results of the tissue burden studies are found in Appendixes H and I.

A complete necropsy and microscopic examination were performed on all rats and mice. The brain, right kidney, liver, lung, spleen, and thymus of all animals at both interim evaluations and all animals surviving until the end of the studies were weighed as were the right testes from males at the 7-month interim evaluation. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed, trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., kidney, ovary, adrenal gland), samples from each organ are examined. Tissues examined microscopically are listed in Table 4.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist reviewed the lung, bronchial and mediastinal lymph nodes, and adrenal gland medulla in rats and the lung, nose, and bronchial lymph nodes in mice for all neoplastic and nonneoplastic lesions. All diagnosed neoplasms from all organs in rats and mice, with the exception of interstitial cell adenomas of the testis in rats, were also reviewed.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the selected tissues and any other tissues for which a disagreement in diagnosis between the laboratory and quality assessment pathologists existed. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologist, or lesions of general interest were presented by the chair to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes or missexed were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3,

C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

Analysis of Neoplasm Incidences

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if the fit of the model was not significantly enhanced. The neoplasm incidences of exposed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

In addition to logistic regression, other methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These methods include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal neoplasms, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals.

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, refer to Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluations, the Fisher exact test, a procedure based on the overall proportion of affected animals, was used.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, spermatid, epididymal spermatozoa, and tissue burden data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973). Because the vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure levels.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database (Haseman *et al.*, 1984, 1985) are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of nickel oxide was assessed by testing the ability of the chemical to increase the frequency of micronucleated erythrocytes in peripheral blood. The protocol for these studies and the results are given in Appendix E.

The genetic toxicity studies of nickel oxide are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the structure and responses of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.

TABLE 4
Experimental Design and Materials and Methods in the Inhalation Studies of Nickel Oxide

16-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
Lovelace Inhalation Toxicology Research Institute (Albuquerque, NM)	Lovelace Inhalation Toxicology Research Institute (Albuquerque, NM)	Lovelace Inhalation Toxicology Research Institute (Albuquerque, NM)
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Frederick Cancer Research Facility (Frederick, MD)	Simonsen Laboratories (Gilroy, CA)	Rats: Taconic Farms (Germantown, NY) Mice: Simonsen Laboratories (Gilroy, CA)
Time Held Before Studies		
19 days (males) or 20 days (females)	19 days (males) or 20 days (females)	11 days
Average Age When Studies Began		
7 weeks	7 weeks	6 weeks
Date of First Dose		
Rats: 27 (males) or 28 (females) January 1986 Mice: 3 (males) or 4 (females) February 1986	Rats: 14 (males) or 15 (females) July 1986 Mice: 21 (males) or 22 (females) July 1986	Rats: 4 April 1988 Mice: 25 April 1988
Duration of Dosing		
6 hours/day, 5 days/week for 16 days	6 hours/day, 5 days/week for 13 weeks (excluding one holiday)	6 hours/day, 5 days/week for 104 weeks (excluding holidays)
Date of Last Dose		
Rats: 11 (males) or 12 (females) February 1986 Mice: 18 (males) or 19 (females) February 1986	Rats: 15 (males) or 17 (females) October 1986 Mice: 21-22 (males) or 23-24 (females) October 1986	Rats 7-Month interim evaluation: 18-19 October 1988 15-Month interim evaluation: 5-6 July 1989 Terminal sacrifice: 30 March 1990 Mice 7-Month interim evaluation: 8-9 November 1988 15-Month interim evaluation: 25-26 July 1989 Terminal sacrifice: 20 April 1990

TABLE 4
Experimental Design and Materials and Methods in the Inhalation Studies of Nickel Oxide (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Necropsy Dates		
Rats: 12 (males) or 13 (females) February 1986 Mice: 19 (males) or 20 (females) February 1986	Rats: 15-16 (males) or 17-18 (females) October 1986 Mice: 22-23 (males) or 24-25 (females) October 1986	Rats 7-Month interim evaluation: 19-20 October 1988 15-Month interim evaluation: 6-7 July 1989 Terminal sacrifice: 6-10 (males) or 2-5 (females) April 1990 Mice 7-Month interim evaluation: 9-10 November 1988 15-Month interim evaluation: 26-27 July 1989 Terminal sacrifice: 1-3 May (males) or 23-30 April (females) 1990
Average Age at Necropsy		
9 weeks	20 weeks	7-Month interim evaluation: 34 weeks 15-Month interim evaluation: 71 weeks Terminal sacrifice: 111 weeks
Size of Study Groups		
Core study: 5 males and 5 females Tissue burden study: 5 males and 5 females	Core study: 10 males and 10 females Tissue burden study: 18 male and 18 female rats; 6 male and 6 female mice	Core study: 7-Month interim evaluation: as many as 7 male and 7 female rats; 5 male and 5 female mice 15-Month interim evaluation: 5 male and 5 female rats and mice 2-Year study: 53 or 54 male and female rats; 67 (0 mg/m^3), 67 (1.25 mg/m^3), 66 (2.5 mg/m^3), and 69 (5 mg/m^3) male and 64, 66, 63, and 64 female mice Tissue burden study: 7-Month interim evaluation: 7 male and 7 female rats; 5 male and 5 female mice 15-Month interim evaluation: 5 male and 5 female rats and mice
Method of Distribution		
Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 16-day studies	Same as 16-day studies

TABLE 4
Experimental Design and Materials and Methods in the Inhalation Studies of Nickel Oxide (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Animals per Cage		
1	1	1
Method of Animal Identification		
Toe clip, ear tag, and location within chamber unit	Tail tattoo, ear tag, and cage location	Rats: Tail tattoo Mice: Tail tattoo and ear tag
Diet		
Zeigler NIH-07 open formula meal diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, except during exposure periods, changed at least once weekly	Zeigler NIH-07 open formula diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, except during exposure periods, changed weekly	Same as 13-week studies
Water Distribution		
Tap water (Albuquerque municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*; checked twice daily	Same as 16-day studies	Same as 16-day studies
Cages		
Stainless steel (Hazleton Systems, Inc., Aberdeen, MD), rotated every 4 exposure days and changed weekly	Same as 16-day studies	Same as 16-day studies
Bedding/Cageboard		
Techboard untreated paper (Shepherd Specialties Paper, Inc., Kalamazoo, MI), changed twice daily	Same as 16-day studies	Same as 16-day studies
Room/Chamber Air Supply Filters		
High efficiency particulate air filter MIL Spec MIL-F-51068C (Flanders, Washington, DC); changed as required	Same as 16-day studies	Same as 16-day studies
Chambers		
Stainless steel (Hazleton Systems, Inc., Aberdeen, MD), changed weekly	Same as 16-day studies	Same as 16-day studies
Chamber Environment		
Temperature: 19.8° to 24.1° C Relative humidity: 13.3% to 96.0% Fluorescent light: 12 hours/day Chamber air: 12 ± 2 changes/hour	Temperature: 20.1° to 27.2° C Relative humidity: 12.3% to 98.0% Fluorescent light: 12 hours/day Chamber air: 12 ± 2 changes/hour	Temperature: 22.1° to 25.7° C Relative humidity: 31.8% to 69.1% Fluorescent light: 12 hours/day Chamber air: 3.68 to 21.32 (rats) and 10.06 to 19.44 (mice) changes/hour

TABLE 4
Experimental Design and Materials and Methods in the Inhalation Studies of Nickel Oxide (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Doses		
Core study: 0, 1.2, 2.5, 5, 10, or 30 mg nickel oxide/m^3 (0, 0.9, 2.0, 3.9, 7.9, or 23.6 mg nickel/m^3) Tissue burden study in rats: 0, 1.2, 5, or 10 mg nickel oxide/m^3 (0, 0.9, 3.9, or 7.9 mg nickel/m^3) Tissue burden study in mice: 0, 1.2, 2.5, and 5 mg nickel oxide/m^3 (0, 0.9, 2.0, or 3.9 mg nickel/m^3)	Core study: 0, 0.6, 1.2, 2.5, 5 or 10 mg nickel oxide/m^3 (0, 0.4, 0.9, 2.0, 3.9, or 7.9 mg nickel/m^3) Tissue burden study: 0, 0.6, 2.5, or 10 mg nickel oxide/m^3 (0, 0.4, 2.0, or 7.9 mg nickel/m^3)	Rats: 0, 0.62, 1.25, or 2.5 mg nickel oxide/m^3 (0, 0.5, 1.0, or 2.0 mg nickel/m^3) Mice: 0, 1.25, 2.5, or 5 mg nickel oxide/m^3 (0, 1.0, 2.0, or 3.9 mg nickel/m^3)
Type and Frequency of Observation		
Observed twice daily; animals were weighed initially, after 4 or 5 days of exposure, and at the end of the studies. Clinical observations were recorded initially and after 5 days of exposure.	Observed twice daily; animals were weighed initially, weekly thereafter, and at the end of the studies. Clinical observations were recorded initially and weekly thereafter.	Observed twice daily; animals were weighed and clinical observations were recorded initially, weekly for 13 weeks, monthly thereafter, and at the end of the studies.
Method of Sacrifice		
Exsanguination under halothane anesthesia	Same as 16-day studies	Exsanguination under carbon dioxide anesthesia
Necropsy		
Necropsy performed on all animals. Organs weighed were brain, heart, right kidney, liver, lung, right testis, and thymus.	Necropsy performed on all animals. Organs weighed were brain, heart, right kidney, liver, lung, right testis and thymus.	Necropsy performed on all animals. Organs weighed at the 7- and 15-month interim evaluations were brain, right kidney, liver, lung, spleen, right testis (7-month interim evaluation only), and thymus.
Clinical Pathology		
None	Blood was collected by cardiac puncture from all core study rats and mice surviving to study termination for hematology. ***Hematology:*** hematocrit, hemoglobin concentration, erythrocytes, mean cell volume, mean cell hemoglobin concentration, total leukocytes and differentials, reticulocytes, and nucleated erythrocytes.	Blood was collected from five male and four to five female rats and mice at the 15-month interim evaluation from the retroorbital sinus for hematology. ***Hematology:*** hematocrit, hemoglobin concentration, erythrocytes, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, total leukocytes and differentials, reticulocytes, and nucleated erythrocytes.

TABLE 4
Experimental Design and Materials and Methods in the Inhalation Studies of Nickel Oxide (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Histopathology		
Complete histopathology was performed on all 0 and 30 mg/m^3 rats and mice. In addition to gross lesions and tissue masses with regional lymph nodes, tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland (rats), epididymis, esophagus, gallbladder (mice), heart, kidney, large intestine (colon, cecum, and rectum) larynx, liver, lung, lymph nodes (bronchial, mandibular, mediastinal, and mesenteric), mammary gland, muscle, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate, salivary gland, seminal vesicle, skin, small intestine (duodenum, jejunum, and ileum), spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. The lung of 1.2, 2.5, 5, and 10 mg/m^3 animals; bronchial lymph nodes and thymus of 5 and 10 mg/m^3 animals; and mediastinal lymph nodes and nasal turbinates of 10 mg/m^3 animals were also examined.	Complete histopathology was performed on all rats and 0 and 10 mg/m^3 mice. In addition to gross lesions and tissue masses with regional lymph nodes, tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland (rats), epididymis, esophagus, gallbladder (mice), heart, kidney, large intestine (colon, cecum, and rectum) larynx, liver, lung, lymph nodes (bronchial, mandibular, mediastinal, and mesenteric), mammary gland, muscle, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate, salivary gland, seminal vesicle, skin, small intestine (duodenum, jejunum, and ileum), spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. The lung, bronchial lymph nodes, and nose were also examined in all other groups of mice.	Complete histopathology was performed on all rats and mice, with the exception of animals evaluated at 7 months in which only kidney, lung, lymph nodes (bronchial and mediastinal), and nasal turbinates were examined. For all others, in addition to gross lesions and tissue masses with regional lymph nodes, tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, rectum), larynx, liver, lung, lymph nodes (bronchial, mandibular, mediastinal, and mesenteric), mammary gland, muscle, nose (3 levels), ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, small intestine (duodenum, jejunum, ileum), spleen, stomach (forestomach and glandular) testis, thymus, thyroid gland, urinary bladder, and uterus.
Tissue Burden Analyses		
Lung and/or kidney (see Appendixes H and I)	Lung (see Appendixes H and I)	Lung (see Appendixes H and I)
Sperm Morphology and Vaginal Cytology Evaluations		
None	At the end of the studies sperm samples were collected from all male animals in the 0, 2.5, 5, and 10 mg/m^3 groups for sperm morphology evaluations. The parameters evaluated were: sperm density, morphology, and motility. The right cauda, right epididymis, and right testis were weighed. Vaginal samples were collected for up to 7 consecutive days prior to the end of the studies from all female animals in the 0, 2.5, 5, and 10 mg/m^3 groups for vaginal cytology evaluations. The parameters evaluated were relative frequency of estrous stages and estrous cycle length.	None

RESULTS

RATS

16-DAY STUDY

All rats survived to the end of the study (Table 5). Final mean body weights and mean body weight gains of exposed male and female rats were similar to those of the controls, and no clinical findings in any group were related to nickel oxide exposure.

TABLE 5
Survival and Body Weights of Rats in the 16-Day Inhalation Study of Nickel Oxide

Dose (mg/m^3)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	143 ± 3	213 ± 5	70 ± 2	
1.2	5/5	144 ± 3	211 ± 4	67 ± 4	99
2.5	5/5	142 ± 5	214 ± 6	72 ± 3	101
5	5/5	144 ± 2	210 ± 4	66 ± 3	99
10	5/5	142 ± 4	210 ± 4	69 ± 3	99
30	5/5	139 ± 5	204 ± 5	65 ± 3	96
Female					
0	5/5	121 ± 2	150 ± 2	28 ± 1	
1.2	5/5	122 ± 3	155 ± 3	32 ± 2	103
2.5	5/5	123 ± 3	154 ± 4	31 ± 3	103
5	5/5	124 ± 1	156 ± 2	32 ± 1	104
10	5/5	124 ± 2	150 ± 2	26 ± 4	101
30	5/5	123 ± 2	149 ± 3	26 ± 4	99

[a] Number of animals surviving at 16 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the control group were not significant by Dunnett's test.

Absolute and relative lung weights of 10 and 30 mg/m^3 males and females were significantly greater than those of the controls (Table F1). At necropsy, chemical-related gross lesions were limited to a slight enlargement of the bronchial lymph nodes in two male and two female rats exposed to 30 mg/m^3. The lymph node enlargement was attributed to lymphoid hyperplasia, which was evident by microscopic examination of the bronchial lymph nodes of most 30 mg/m^3 males and females. In addition to those in the lymph nodes, histopathologic changes were also present in the lungs and nose (Table 6). In most rats exposed to 10 or 30 mg/m^3, inflammatory cell infiltrates in the alveolar interstitium, foci of acute inflammation (neutrophilic infiltrates), and an increase in the number of alveolar macrophages in the lungs were observed. Pigment, consisting of densely stained black particles, was present in the cytoplasm of alveolar macrophages as well as extracellularly within the alveolar spaces. At the lower exposure concentrations, histopathologic changes were limited to accumulation of alveolar macrophages and the presence of black pigment particles in the lung. Minimal atrophy of the olfactory epithelium in the nose was also present in one male and one female exposed to 30 mg/m^3.

TABLE 6
Incidences of Selected Nonneoplastic Lesions in Rats in the 16-Day Inhalation Study of Nickel Oxide

	0 mg/m^3	1.2 mg/m^3	2.5 mg/m^3	5 mg/m^3	10 mg/m^3	30 mg/m^3
Male						
Lung[a]	5	5	5	5	5	5
Alveolar Macrophage Hyperplasia[b]	0	2 (1.0)[c]	3 (1.0)	5** (1.0)	5** (1.6)	5** (3.0)
Inflammation	0	0	0	0	2 (1.0)	5** (2.8)
Interstitial Infiltrate	0	0	0	0	0	5** (2.8)
Pigment	0	5** (1.0)	5** (1.0)	5** (2.0)	5** (2.2)	5** (3.0)
Lymph Node, Bronchial	4	—[d]	—	3	3	4
Hyperplasia	0			0	1 (1.0)	4* (3.0)
Nose	5	—	—	—	5	5
Atrophy, Olfactory Epithelium	0				0	1 (1.0)
Female						
Lung	5	5	5	5	5	5
Alveolar Macrophage Hyperplasia	0	0	0	4* (1.0)	5** (2.0)	5** (3.0)
Inflammation	0	0	0	0	5** (2.0)	5** (2.8)
Interstitial Infiltrate	0	0	0	0	5** (2.0)	5** (3.0)
Pigment	0	5** (1.0)	5** (1.0)	5** (1.8)	5** (2.8)	5** (3.0)
Lymph Node, Bronchial	4	—	—	4	4	4
Hyperplasia	0			0	1 (2.0)	3 (3.0)
Nose	5	—	—	—	5	5
Atrophy, Olfactory Epithelium	0				0	1 (1.0)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[d] Tissue not examined at this exposure concentration

Nickel concentrations in the lungs of 1.2, 5, and 10 mg/m^3 males and females were greater than those in the controls and increased with exposure concentration, and the absolute lung weights of these 10 mg/m^3 males and females were significantly greater than those of the controls (Tables 7 and H1). Nickel concentrations in the kidney of 10 mg/m^3 male and female rats were below the limit of detection; however, the absolute kidney weight of these females was significantly greater than that of the controls (Table H2).

Because of the severity of lung lesions in rats exposed to 30 mg/m^3, 10 mg/m^3 was selected as the highest exposure concentration for the 13-week study.

TABLE 7
Lung Weight and Lung Burden in Rats in the 16-Day Inhalation Study of Nickel Oxide[a]

	0 mg/m^3	1.2 mg/m^3	5 mg/m^3	10 mg/m^3
n	5	5	5	5
Male				
Absolute lung wt (g)	0.856 ± 0.047	0.870 ± 0.046	0.822 ± 0.041	1.068 ± 0.056*
μg Ni/lung	—[b]	36 ± 1.3**	88 ± 4.8**	284 ± 9.7**
μg Ni/g lung	—	42 ± 2.8**	108 ± 4.3**	267 ± 12.3**
μg Ni/g control lung	—	42 ± 1.6**	103 ± 5.6**	331 ± 11.4**
Female				
Absolute lung wt (g)	0.739 ± 0.028	0.704 ± 0.017	0.731 ± 0.040	0.861 ± 0.025*
μg Ni/lung	—	38 ± 4.8**	88 ± 3.3**	293 ± 13.4**
μg Ni/g lung	—	54 ± 5.7**	122 ± 10.3**	340 ± 10.4**
μg Ni/g control lung	—	52 ± 6.5**	119 ± 4.5**	396 ± 18.2**

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test (lung weight) or Shirley's test (lung burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error
[b] Results were below 0.182 μg Ni (the limit of detection), or below the level of quantitation.

13-WEEK STUDY

One male rat exposed to 2.5 mg nickel oxide/m^3 died during week 3 of the study; this death was not considered to be exposure related (Table 8). Final mean body weights and mean body weight gains of exposed males and females were similar to those of the controls. There were no consistent clinical findings in any group that were related to nickel oxide exposure.

TABLE 8
Survival and Body Weights of Rats in the 13-Week Inhalation Study of Nickel Oxide

Dose (mg/m^3)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	128 ± 3	306 ± 7	179 ± 5	
0.6	10/10	132 ± 4	317 ± 6	185 ± 6	103
1.2	10/10	130 ± 4	319 ± 7	189 ± 5	104
2.5	9/10[c]	131 ± 4	303 ± 6	171 ± 5	99
5	10/10	130 ± 4	314 ± 5	184 ± 6	102
10	10/10	127 ± 3	308 ± 6	181 ± 5	100
Female					
0	10/10	110 ± 3	190 ± 5	80 ± 3	
0.6	10/10	112 ± 3	192 ± 3	80 ± 3	101
1.2	10/10	106 ± 2	193 ± 3	87 ± 4	101
2.5	10/10	107 ± 3	186 ± 4	79 ± 3	98
5	10/10	100 ± 3	187 ± 4	87 ± 3	98
10	10/10	110 ± 3	190 ± 4	81 ± 3	100

[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. Differences from the control group were not significant by Dunnett's test.
[c] Week of death: 3

Hematology results are presented in Table G1. In general, there were minimal to mild differences, and females were affected more than males. A mature neutrophilia was indicated by greater segmented neutrophil counts in 1.2, 2.5, 5, and 10 mg/m^3 males and all exposed females. Monocyte counts in 2.5, 5, and 10 mg/m^3 females were mildly greater than that in the controls. There was microscopic evidence of chronic active pulmonary inflammation in 2.5, 5, and 10 mg/m^3 males and females, and this could account for the neutrophilia and monocytosis. Increased tissue demand for granulocytes due to inflammation causes increased bone marrow production and release and can increase the intravascular life span of neutrophils resulting in neutrophilia. Monocytosis can also result from inflammation, particularly a chronic inflammatory process. However, neutrophilia occurred at exposure concentrations at which no microscopic evidence of inflammation was seen. Thus, mechanisms that alter granulopoiesis and/or rate of release from the bone marrow, redistribute neutrophils between the marginal and the circulating pools, or increase the intravascular neutrophil life span could be considered. Lymphocytosis was indicated by lymphocyte counts in 2.5, 5, and 10 mg/m^3 females that were greater than that in the controls. The lymphocytosis may be a reflection of the bronchial and mediastinal lymph node hyperplasia observed in these exposure groups. However, stimulation of lymphopoiesis may not result in lymphocytosis, and other mechanisms altering lymphocyte margination or homing, tissue migration, and recirculation may be involved. Total leukocyte counts in 1.2 and 10 mg/m^3 males and in females exposed to 1.2 mg/m^3 or higher were greater than those in the controls and were a reflection of the increased neutrophil, lymphocyte, and monocyte counts.

Hematocrit, hemoglobin concentration, and erythrocyte counts in 10 mg/m^3 males and in most exposed groups of females were minimally to mildly greater than those in the controls. These differences were accompanied by mean cell volumes in 5 mg/m^3 males and in 1.2 mg/m^3 and higher females that were minimally less than those in the controls. Mean cell hemoglobin concentrations in 2.5 mg/m^3 males and all exposed groups of females were minimally greater than those in the controls. Increases in mean cell hemoglobin concentration have been related to erythrocyte hemolysis (*in vivo* or *in vitro*), alterations in the hemoglobin concentration or hematocrit, or an artifact (e.g., lipemia, Heinz bodies). The higher hematocrit values, hemoglobin concentrations, and erythrocyte counts could be consistent with dehydration (relative erythrocytosis) or with increased erythropoietin production as the result of tissue hypoxia (secondary erythrocytosis). Secondary erythrocytosis has been observed with pulmonary or cardiovascular disease, altered erythrocyte/hemoglobin oxygen transport, and reduced atmospheric oxygen. In this study, pulmonary lesions were observed microscopically in 2.5, 5, and 10 mg/m^3 males and females, and this could account for the increases observed. Lower mean cell volume has been associated with metabolic alterations related to iron, copper, and pyridoxine deficiency. Total nucleated erythrocyte counts in 5 mg/m^3 males and all exposed females were greater than those in the controls. Reticulocyte counts were not affected, and this is consistent with mild relative erythrocytosis or with a very mild increase in erythropoiesis. Differences in nucleated erythrocyte counts were not accompanied by anemia or by corresponding differences in reticulocyte counts. Nickel is a transition metal, as are cobalt and iron. Excess cobalt can induce erythrocytosis due to increased erythropoietin production, and iron is essential for heme synthesis. Thus, the presence of excess nickel may have altered normal biological activities associated with transition metals and could account for some of the differences that occurred (e.g., the minimal erythrocytosis and lower mean cell volume).

Sperm concentration in 10 mg/m^3 males was significantly lower than that in controls (Table J1). There were no significant differences in vaginal cytology between control and exposed females.

Absolute and relative lung weights of all exposed groups of rats (except absolute lung weight of 0.6 mg/m^3 females) were significantly greater than those of controls (Table F2). Other organ weight differences were considered incidental and unrelated to nickel oxide exposure. Chemical-related lesions in the lung and in the bronchial and mediastinal lymph nodes were identified through gross examination at necropsy. When the thoracic cavity was opened, the lungs of rats exposed to 10 mg/m^3 failed to collapse to the extent typically observed in control

animals. Multiple pale or white foci, 1 to 2 mm in diameter, were scattered throughout the lung parenchyma in one or more male rats in each exposure group and in most male and female rats exposed to 2.5, 5, or 10 mg/m^3. These lung foci were generally fewer in number and smaller at lower exposure concentrations. The lymph nodes associated with the respiratory tract were enlarged in most male and female rats exposed to 5 or 10 mg/m^3.

Chemical-related histopathologic lesions were present in the lung and in the lymph nodes associated with the respiratory tract of exposed males and females (Table 9). The lymph node enlargement was

TABLE 9
Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Inhalation Study of Nickel Oxide

	0 mg/m^3	0.6 mg/m^3	1.2 mg/m^3	2.5 mg/m^3	5 mg/m^3	10 mg/m^3
Male						
Lung[a]	10	10	10	9	10	10
Alveolar Macrophage Hyperplasia[b]	0	10** (1.0)[c]	10** (1.0)	9** (1.0)	10** (1.5)	10** (2.5)
Inflammation, Chronic Active	0	0	0	2 (1.0)	10** (1.4)	10** (3.0)
Inflammation, Granulomatous	0	0	0	0	3 (2.0)	2 (3.0)
Interstitial Infiltrate	0	0	1 (1.0)	2 (1.0)	10** (1.4)	10** (2.1)
Pigment	0	6** (1.0)	7** (1.0)	9** (1.0)	9** (1.0)	10** (1.8)
Lymph Node, Bronchial	8	9	10	8	10	10
Hyperplasia	0	0	0	2 (1.0)	9** (1.6)	10** (2.7)
Pigment	0	0	0	7** (1.0)	10** (1.0)	10** (1.0)
Lymph Node, Mediastinal	9	8	8	8	10	10
Hyperplasia	0	0	0	2 (1.0)	5* (1.4)	10** (2.5)
Pigment	0	0	0	4* (1.0)	6** (1.0)	5* (1.0)
Female						
Lung	10	10	10	10	10	10
Alveolar Macrophage Hyperplasia	0	10** (1.0)	8** (1.0)	10** (1.0)	10** (1.4)	10** (2.2)
Inflammation, Chronic Active	0	0	0	1 (1.0)	7** (1.3)	7** (2.7)
Inflammation, Granulomatous	0	0	0	0	4* (2.1)	4* (2.0)
Interstitial Infiltrate	0	0	0	2 (1.0)	10** (1.2)	10** (1.8)
Pigment	0	0	4* (1.0)	8** (1.0)	8** (1.0)	10** (1.2)
Lymph Node, Bronchial	7	7	10	7	10	10
Hyperplasia	0	0	0	0	8** (1.5)	10** (2.6)
Pigment	0	0	0	4* (1.0)	8** (1.0)	10** (1.0)
Lymph Node, Mediastinal	9	9	8	10	9	10
Hyperplasia	0	0	0	1 (1.0)	5* (1.4)	9** (2.2)
Pigment	0	0	0	2 (1.0)	9** (1.0)	8** (1.0)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

attributed to lymphoid hyperplasia characterized by an increase in the number of lymphocytes, primarily in the paracortical areas of the lymph nodes. Lymphoid hyperplasia was commonly present in rats exposed to 5 or 10 mg/m^3 and also occurred in a few 2.5 mg/m^3 rats. Densely stained black pigment particles and aggregates of these pigment particles were present in the lymph nodes of males and females exposed to 2.5, 5, or 10 mg/m^3. There were exposure-related inflammatory lesions and pigment in the lungs of males and females. At the lower exposures of 0.6, 1.2, and 2.5 mg/m^3, there was only a minimally detectable increase in the number of macrophages within the alveoli; minimal interstitial or chronic active inflammation was present in a few rats. Pigment particles were present in the cytoplasm of alveolar macrophages as well as extracellularly within the alveolar spaces. At 5 and 10 mg/m^3, the severity and spectrum of inflammatory changes in the lung were increased. Inflammatory lesions included minimal to mild interstitial infiltrates of lymphocytes around blood vessels and chronic active inflammation characterized by a mild thickening of alveolar septa with a mixture of neutrophils and mononuclear inflammatory cells. Adjacent to these foci of inflammation, type II cells were often enlarged. Granulomatous inflammation also occurred in a few rats and consisted of larger, focal aggregates of epithelioid macrophages within the alveoli or interstitial areas.

At 4 and 9 weeks and at the end of the 13-week study, nickel concentrations in the lung of 0.6, 2.5, and 10 mg/m^3 males were significantly greater than those in the controls, and the nickel concentrations increased with exposure concentration (Tables 10 and H3). At 13 weeks, the absolute lung weights of 2.5 and 10 mg/m^3 males were significantly greater than that of the controls.

TABLE 10
Lung Weight and Lung Burden in Male Rats in the 13-Week Inhalation Study of Nickel Oxide[a]

	0 mg/m^3	0.6 mg/m^3	2.5 mg/m^3	10 mg/m^3
n	6	6	6	6
4 weeks				
μg Ni/g lung	—[b]	33 ± 2.3**	110 ± 6.6**	263 ± 18.5**
9 weeks				
μg Ni/g lung	—	53 ± 6.8**	143 ± 27.9**	400 ± 31.2**
13 weeks				
Absolute lung wt (g)	0.954 ± 0.043	1.082 ± 0.028	1.534 ± 0.032**	2.108 ± 0.097**
μg Ni/lung	—	86 ± 6.0**	276 ± 34.6**	1,092 ± 63.1**
μg Ni/g lung	—	80 ± 5.5**	181 ± 25.6**	524 ± 38.2**
μg Ni/g control lung	—	91 ± 6.3**	289 ± 36.3**	1,146 ± 66.2**

** Significantly different ($P \leq 0.01$) from the control group by Williams' test (lung weight) or Shirley's test (lung burden parameters)
[a] Mean ± standard error
[b] Results were below 0.301 μg Ni (the limit of detection), or below the level of quantitation.

Dose Selection Rationale: Based on the increased severity and wider spectrum of inflammatory lesions of the lung and increased lung weights in males and females exposed to 5 and 10 mg/m^3 in the 13-week study, nickel oxide exposure concentrations selected for the 2-year inhalation study in rats were 0.62, 1.25, and 2.5 mg/m^3.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 11 and in the Kaplan-Meier survival curves in Figure 2. Survival of exposed male and female rats was similar to that of the controls.

TABLE 11
Survival of Rats in the 2-Year Inhalation Study of Nickel Oxide

	0 mg/m^3	0.62 mg/m^3	1.25 mg/m^3	2.5 mg/m^3
Male				
Animals initially in study	65	65	65	65
7-Month interim evaluation[a]	6	7	7	7
15-Month interim evaluation[a]	5	5	5	5
Missexed[a]	0	0	0	1
Moribund	39	35	32	36
Natural deaths	1	3	6	4
Animals surviving to study termination	14	15	15[e]	12[e]
Percent probability of survival at end of study[b]	26	28	28	23
Mean survival (days)[c]	592	594	582	582
Survival analysis[d]	P=0.563	P=0.772N	P=1.000N	P=0.720
Female				
Animals initially in study	65	65	65	65
7-Month interim evaluation[a]	7	7	7	6
15-Month interim evaluation[a]	5	5	5	5
Moribund	27	24	27	25
Natural deaths	5	3	6	3
Animals surviving to study termination	21	26	20	26
Percent probability of survival at end of study	40	49	38	48
Mean survival (days)	594	607	592	597
Survival analysis	P=0.834N	P=0.392N	P=0.921	P=0.657N

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on the first day of terminal sacrifice
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed columns. A negative trend or a lower mortality in an exposure group is indicated by N.
[e] Includes one animal that died during the last week of the study.

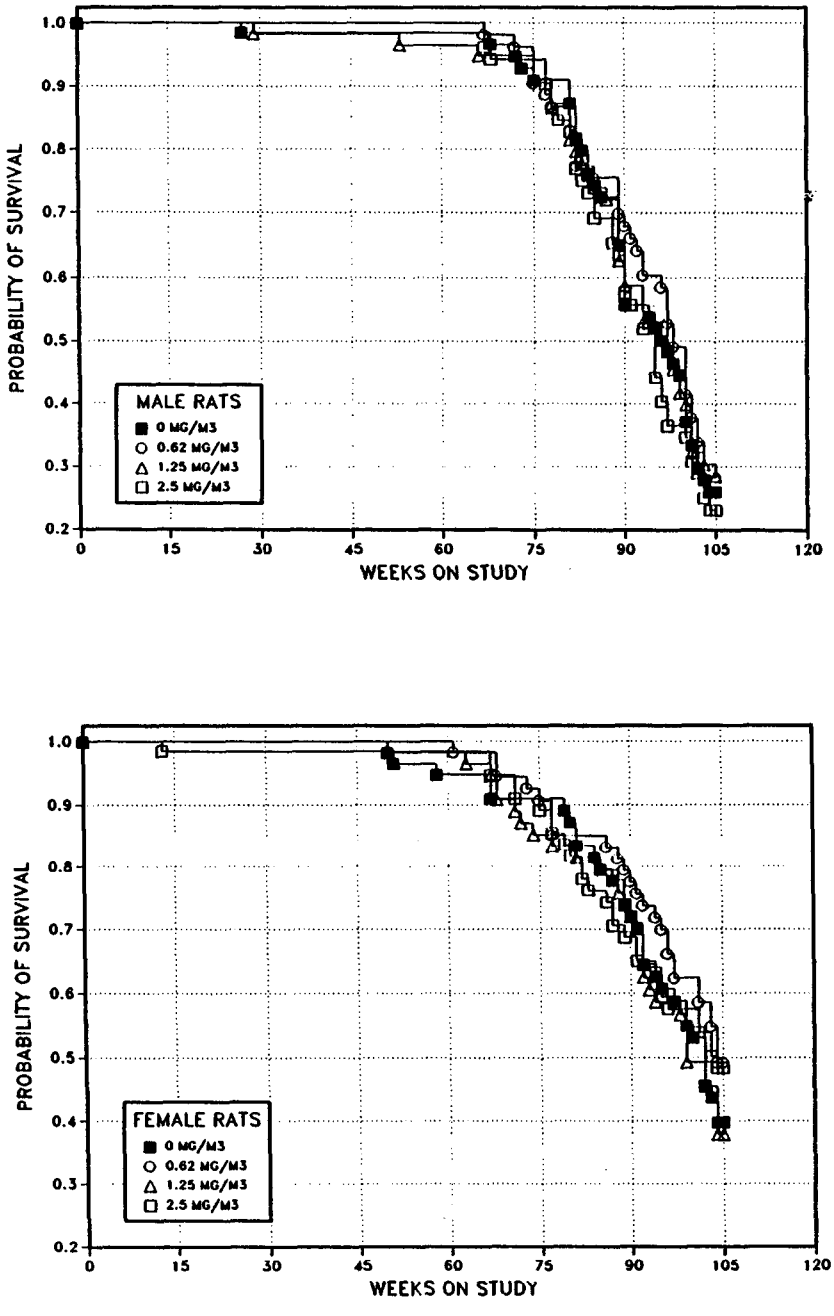

FIGURE 2
Kaplan-Meier Survival Curves for Rats Administered Nickel Oxide by Inhalation for 2 Years

Body Weights and Clinical Findings

Mean body weights of males and females exposed to 0.62 mg/m^3 and males exposed to 1.25 mg/m^3 were similar to those of the controls throughout the study (Figure 3 and Tables 12 and 13). Mean body weights of females exposed to 1.25 mg/m^3 and males and females exposed to 2.5 mg/m^3 were slightly less than those of the controls during the second year of the study. No chemical-related clinical findings were observed in male or female rats during the 2-year study.

Hematology

No chemical-related differences in hematology parameters were observed in male or female rats at the 15-month interim evaluation (Table G2).

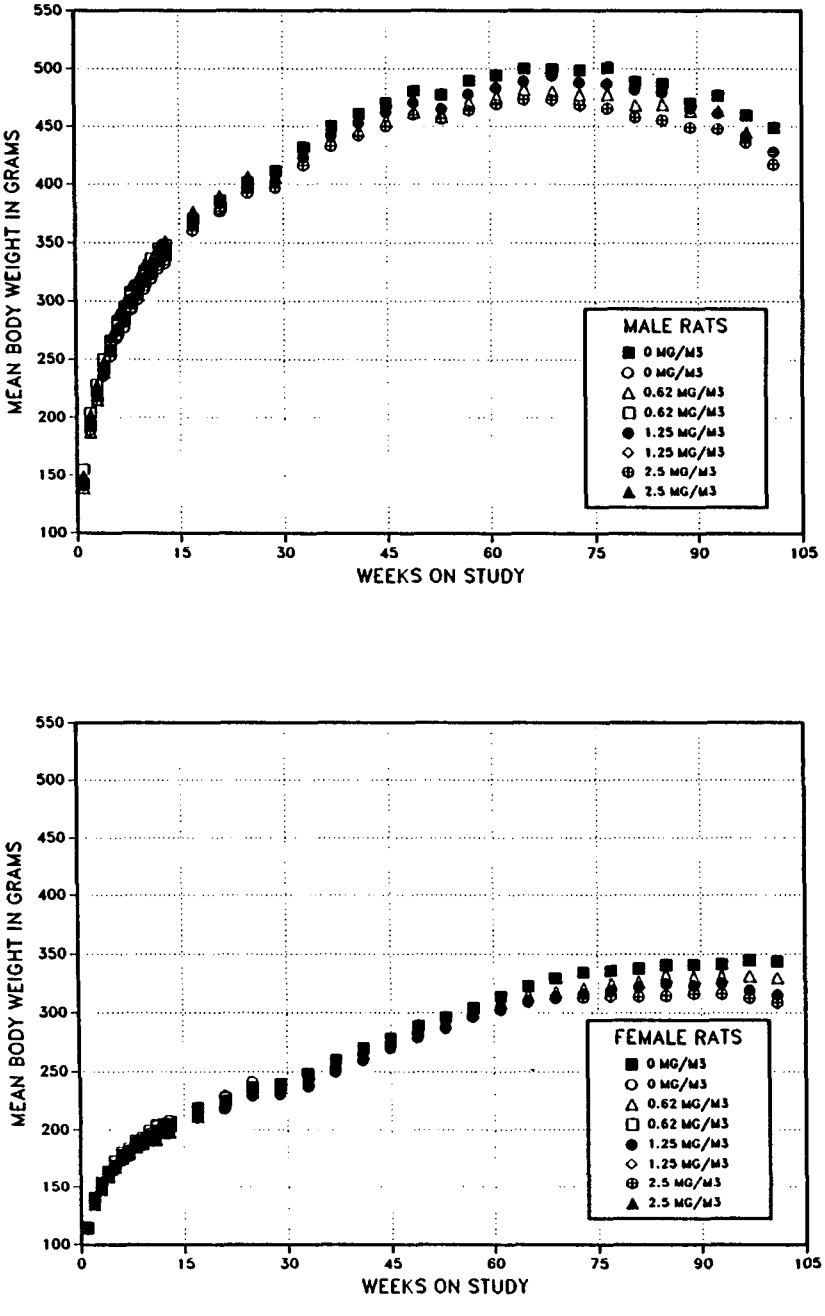

FIGURE 3
Growth Curves for Rats Administered Nickel Oxide by Inhalation for 2 Years

TABLE 12
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Nickel Oxide

Weeks on Study	0 mg/m³ Av. Wt. (g)	0 mg/m³ No. of Survivors	0.62 mg/m³ Av. Wt. (g)	0.62 mg/m³ Wt. (% of controls)	0.62 mg/m³ No. of Survivors	1.25 mg/m³ Av. Wt. (g)	1.25 mg/m³ Wt. (% of controls)	1.25 mg/m³ No. of Survivors	2.5 mg/m³ Av. Wt. (g)	2.5 mg/m³ Wt. (% of controls)	2.5 mg/m³ No. of Survivors
1	143	65	141	98	65	141	99	65	142	99	65
2	193	65	189	98	65	193	100	65	191	99	65
3	219	65	216	99	65	222	102	65	216	99	65
4	241	65	240	100	65	241	100	65	237	98	64
5	257	65	259	101	65	258	100	65	254	99	64
6	274	65	276	101	65	276	101	65	273	100	64
7	284	65	288	102	65	287	101	65	283	100	64
8	297	65	299	101	65	301	101	65	296	100	64
9	306	65	307	100	65	308	101	65	304	99	64
10	316	65	318	101	65	320	101	65	315	100	64
11	324	65	327	101	65	326	101	65	321	99	64
12	333	65	336	101	65	335	101	65	332	100	64
13	340	65	340	100	65	339	100	65	337	99	64
17	368	65	366	100	65	366	100	65	362	98	64
21	385	65	382	99	65	384	100	65	378	98	64
25	401	65	398	99	65	399	99	65	394	98	64
29[a]	411	58	406	99	58	402	98	58	397	96	57
33	432	58	421	98	58	424	98	57	416	96	57
37	451	58	438	97	58	442	98	57	433	96	57
41	461	58	446	97	58	453	98	57	442	96	57
45	470	58	455	97	58	462	98	57	450	96	57
49	481	58	462	96	58	471	98	57	460	96	57
53	478	58	459	96	58	466	98	56	457	96	57
57	490	58	471	96	58	478	98	56	464	95	57
61	494	58	476	96	58	484	98	56	469	95	57
65	500	58	482	96	58	489	98	56	473	95	57
69[a]	499	52	481	96	52	494	99	50	473	95	49
73	499	50	478	96	51	488	98	50	468	94	49
77	501	49	477	95	48	487	97	48	465	93	48
81	489	49	468	96	45	482	99	45	458	94	43
85	487	40	469	96	41	480	99	39	456	94	37
89	471	37	464	99	38	466	99	33	449	95	33
93	477	30	464	97	32	461	97	28	448	94	28
97	460	26	445	97	30	442	96	26	436	95	20
101	449	18	449	100	20	428	95	20	417	93	18
Mean for weeks											
1-13	271		272	100		273	101		269	99	
14-52	429		419	98		423	99		415	97	
53-101	484		468	97		473	98		456	94	

[a] Interim evaluations occurred during weeks 29 and 66.

TABLE 13
Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Nickel Oxide

Weeks on Study	0 mg/m³ Av. Wt. (g)	0 mg/m³ No. of Survivors	0.62 mg/m³ Av. Wt. (g)	0.62 mg/m³ Wt. (% of controls)	0.62 mg/m³ No. of Survivors	1.25 mg/m³ Av. Wt. (g)	1.25 mg/m³ Wt. (% of controls)	1.25 mg/m³ No. of Survivors	2.5 mg/m³ Av. Wt. (g)	2.5 mg/m³ Wt. (% of controls)	2.5 mg/m³ No. of Survivors
1	115	65	115	100	65	114	99	65	114	99	65
2	140	65	139	99	65	139	99	65	137	98	65
3	153	65	151	99	65	151	99	65	149	97	65
4	163	65	161	99	65	159	98	65	159	98	65
5	169	65	168	99	65	165	98	65	167	99	65
6	179	65	176	99	65	174	97	65	176	99	65
7	181	65	181	100	65	177	98	65	180	99	65
8	188	65	187	99	65	185	98	65	186	99	65
9	191	65	189	99	65	187	98	65	187	98	65
10	195	65	194	99	65	193	99	65	192	99	65
11	200	65	199	100	65	195	98	65	194	97	65
12	202	65	202	100	65	201	99	65	200	99	65
13	205	65	204	99	65	202	98	65	203	99	65
17	217	65	215	99	65	211	97	65	213	98	64
21	226	65	223	99	65	218	97	65	221	98	64
25	237	65	233	98	65	230	97	65	233	98	64
29[a]	239	58	237	99	58	231	96	58	235	98	58
33	248	58	243	98	58	238	96	58	243	98	58
37	260	58	255	98	58	250	96	58	253	97	58
41	270	58	265	98	58	260	96	58	265	98	58
45	278	58	276	99	58	271	97	58	272	98	58
49	289	58	286	99	58	279	96	58	283	98	58
53	296	56	292	99	58	287	97	57	287	97	58
57	304	56	301	99	58	297	98	57	297	98	58
61	314	55	308	98	57	305	97	57	303	96	58
65	323	55	315	98	57	311	96	56	309	96	58
69[a]	330	48	318	97	50	314	95	48	313	95	51
73	335	48	321	96	49	316	95	46	313	94	49
77	336	48	325	97	45	320	95	44	314	94	48
81	338	44	326	97	45	323	95	43	314	93	44
85	341	42	332	97	45	325	95	42	315	92	41
89	341	39	330	97	43	323	95	39	316	93	37
93	341	34	331	97	39	325	95	32	316	93	35
97	345	31	332	96	33	319	93	31	312	91	31
101	344	28	330	96	32	316	92	26	308	90	29
Mean for weeks											
1-13	175		174	99		172	98		173	99	
14-52	252		248	98		243	96		246	98	
53-101	330		320	97		314	95		309	94	

[a] Interim evaluations occurred during weeks 29 and 66.

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of nonneoplastic lesions of the lung, lymph nodes, and adrenal medulla and neoplasms of the lung and adrenal medulla. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Lung: Absolute and relative lung weights of males exposed to 1.25 or 2.5 mg/m^3 and of exposed females were significantly greater than those of the controls at 7 months (Table F3). At 15 months, absolute and relative lung weights of males and females exposed to 1.25 or 2.5 mg/m^3 were significantly greater than those of the controls (Table F4). At 2 years, the incidence of alveolar/bronchiolar carcinoma in 1.25 mg/m^3 females was significantly greater than that of the controls (Tables 14 and B3). There are no incidences of alveolar/bronchiolar carcinoma in historical control females from inhalation studies, and the incidence in the 1.25 mg/m^3 females exceeds the historical control range from feed studies (Tables 14 and B4a). There were exposure-related increases in the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in males and females. The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in 1.25 mg/m^3 males and females and 2.5 mg/m^3 females exceeded historical control ranges from inhalation studies (Tables 14, A4a, and B4a).

Alveolar/bronchiolar carcinomas had neoplastic cells arranged in mixtures of alveolar, papillary, and tubular structures, and the cells often formed multiple layers or solid clusters. A few carcinomas contained small to moderate amounts of dense fibrous tissue (scirrhous reaction). A few carcinomas, particularly those with scirrhous reaction, had large, moderately to highly pleomorphic cells. Carcinomas with squamous differentiation consisted of a mixture of an alveolar/bronchiolar epithelial component and a stratified squamous epithelial component (Plate 1). These carcinomas presumably originated from the alveolar/bronchiolar epithelium, and the stratified squamous epithelial component arose through squamous differentiation. The stratified squamous component in five of these alveolar/bronchiolar carcinomas in exposed rats was the predominant component, highly proliferative, and clearly neoplastic. This pronounced squamous component is not typical of alveolar/bronchiolar carcinomas arising spontaneously in nonexposed rats; however, the fibrous tissue component and the squamous differentiation observed in some of these neoplasms have also been observed in rats in other studies of inhaled particulates (e.g. talc; NTP, 1993a). Alveolar/bronchiolar adenoma consisted of relatively uniform simple cuboidal or columnar epithelium arranged in papillary or pseudoalveolar patterns that focally distorted or replaced normal alveolar architecture (Plate 2). Adenomas were usually visible macroscopically in histopathologic specimens. The severity of the inflammatory alterations in the lungs of exposed rats obscured the gross identification of most of these neoplasms at necropsy.

One male and one female rat exposed to 2.5 mg/m^3 had a squamous cyst, and there was one instance of squamous metaplasia in the lung of a 0.62 mg/m^3 male (Tables 14, A5, and B5). A squamous cyst has a well-differentiated, stratified squamous epithelial wall and a central lumen containing keratin. Squamous metaplasia in the lung is the focal replacement of alveolar pneumocytes by well-differentiated squamous epithelium.

The incidence of atypical alveolar epithelial hyperplasia generally increased with exposure concentration in males and females at 2 years. Both focal and atypical alveolar epithelial hyperplasias were considered a part of the morphologic continuum toward neoplasia. Focal alveolar epithelial hyperplasia consisted of foci where basophilic cuboidal epithelial cells, rather than type I cells, lined alveolar septa that maintained normal architecture. Atypical alveolar epithelial hyperplasia consisted of focal hyperplasia in which lining cells had increased basophilia and less uniformity in size, shape, and alignment. Some hyperplasias occurred near foci of inflammation, but the hyperplasia extended a considerable distance away from the inflammation; these were considered to be a chemical-related effect separate from the inflammation.

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Rats in the 2-Year Inhalation Study of Nickel Oxide

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Male				
7-Month Interim Evaluation				
Lung[a]	6	7	7	7
Inflammation, Chronic[b]	3 (1.0)[c]	0	7 (2.0)	7 (1.7)
Alveolus, Pigmentation	0	6** (1.0)	7** (1.0)	6** (1.0)
15-Month Interim Evaluation				
Lung	5	5	5	5
Inflammation, Chronic	4 (1.0)	5 (1.0)	5 (2.2)	5 (2.2)
Alveolus, Pigmentation	0	5** (1.0)	5** (1.2)	5** (2.0)
2-Year Study				
Lung	54	53	53	52
Inflammation, Chronic	28 (1.1)	53** (1.6)	53** (2.1)	52** (2.6)
Alveolar Epithelium, Hyperplasia, Focal or Atypical	0	2 (2.0)	5 (1.8)	0
Alveolar Epithelium, Squamous Metaplasia	0	1 (1.0)	0	0
Alveolus, Pigmentation	1 (1.0)	53** (1.3)	53** (1.8)	52** (2.1)
Squamous Cyst	0	0	0	1
Alveolar/bronchiolar Adenoma	0	1	3	2
Alveolar/bronchiolar Carcinoma, Squamous Differentiation	0	0	2	0
Alveolar/bronchiolar Carcinoma (Includes Squamous Differentiation)	0	0	3	2
Alveolar/bronchiolar Adenoma or Carcinoma	0	1	6*	4*
Squamous Cell Carcinoma	1	0	0	0
Alveolar/bronchiolar Adenoma or Carcinoma or Squamous Cell Carcinoma[d]				
Overall rate[e]	1/54 (2%)	1/53 (2%)	6/53 (11%)	4/52 (8%)
Adjusted rate[f]	7.1%	2.6%	27.7%	23.7%
Terminal rate[g]	1/14 (7%)	0/15 (0%)	3/15 (20%)	2/12 (17%)
First incidence	733 (T)	623	567	633
Logistic regression test[h]	P=0.062	P=0.760N	P=0.054	P=0.141
Female				
7-Month Interim Evaluation				
Lung	7	7	7	6
Inflammation, Chronic	1 (1.0)	0	7** (1.1)	6** (1.0)
Alveolus, Pigmentation	0	5* (1.0)	7** (1.0)	6** (1.0)

(continued)

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Female (continued)				
15-Month Interim Evaluation				
Lung	5	5	5	5
Inflammation, Chronic	3 (1.0)	4 (1.0)	5 (2.2)	5 (2.4)
Alveolus, Pigmentation	0	5** (1.0)	5** (1.2)	5** (1.2)
2-Year Study				
Lung	53	53	53	54
Inflammation, Chronic	18 (1.1)	52** (1.7)	53** (2.4)	54** (2.4)
Alveolar Epithelium, Hyperplasia, Focal or Atypical	2 (2.0)	1 (2.0)	6 (2.5)	6 (1.5)
Alveolus, Pigmentation	0	52** (1.7)	53** (2.1)	54** (2.0)
Squamous Cyst	0	0	0	1
Alveolar/bronchiolar Adenoma (Multiple)	0	0	0	1
Alveolar/bronchiolar Adenoma (Single or Multiple)	1	0	1	4
Alveolar/bronchiolar Carcinoma, Squamous Differentiation	0	0	2	1
Alveolar/bronchiolar Carcinoma (Includes Squamous Differentiation)	0	0	5*	1
Alveolar/bronchiolar Adenoma or Carcinoma[i]				
Overall rate	1/53 (2%)	0/53 (0%)	6/53 (11%)	5/54 (9%)
Adjusted rate	4.8%	0.0%	24.7%	19.2%
Terminal rate	1/21 (5%)	0/26 (0%)	4/20 (20%)	5/26 (19%)
First incidence	729 (T)	—[j]	643	729 (T)
Logistic regression test	P=0.022	P=0.457N	P=0.053	P=0.152

(T)Terminal sacrifice
* Significantly different (P≤0.05) from the control group by the Fisher exact test (interim evaluations) or the logistic regression test (2-year study)
** P≤0.01
[a] Number of animals with lung examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[d] Historical incidence for 2-year NTP inhalation studies with untreated control groups (mean ± standard deviation): 27/703 (3.8% ± 3.8%); range 0%-10%. Feed studies: 39/1,200 (3.3% ± 2.0%); range 0%-8%
[e] Number of animals with neoplasm per number of animals with lung examined microscopically
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[g] Observed incidence in animals surviving until the end of the study
[h] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to the pairwise comparisons between the controls and that exposure group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposure group is indicated by N.
[i] Historical incidence for 2-year NTP inhalation studies: 8/700 (1.1% ± 1.5%); range 0%-4% (includes squamous cell carcinoma). Feed studies: 25/1,201 (2.1% ± 2.2%); range 0%-10%
[j] Not applicable; no neoplasms in animal group

Chronic inflammation of the lung was observed in most exposed animals at 7 and 15 months and at 2 years, and the incidences in exposed males and females at 2 years were significantly greater than those in the controls (Tables 14, A5, and B5). The incidences of pigmentation in the alveoli of exposed groups of males and females were significantly greater than those of the controls at 7 and 15 months and at 2 years. The severity of this pigmentation generally increased with increasing exposure concentration. Pigmentation in the lungs of exposed rats was finely granular and black. It was clearly related to nickel oxide exposure and could be differentiated from the occasional coarser granules of endogenous golden brown to greenish-brown hemosiderin pigment. In exposed rats, most or all alveolar lumens contained small to moderate amounts of eosinophilic granular material or irregular aggregates of homogeneous eosinophilic material (proteinosis), and in some lungs this eosinophilic material was the predominant component of the inflammation.

Chronic inflammation also included alveolar macrophages scattered within the lumens of many alveoli (Plate 3). The number of alveoli containing macrophages and the number of macrophages within alveoli increased with increasing severity of inflammation. Some alveolar macrophages resembled those normally seen in the lung, but most were enlarged with a moderate to abundant amount of pale vacuolated cytoplasm. Multiple focal clusters of alveoli filled with accumulations of inflammatory cells (macrophages sometimes mixed with small to moderate numbers of neutrophils) and debris were seen commonly, often in the periphery of the lobes adjacent to the pleural surface. Hyperplasia of alveolar epithelial cells (presumably of type II cells) was usually seen in alveoli containing inflammatory exudate, and was not diagnosed separately since it, was a regenerative response secondary to the inflammation. Varying amounts of parenchymal and subpleural fibrosis were present within these inflammatory foci and, in some cases, the fibrosis was severe and had replaced much of the alveolar structure. Clear slit-like spaces, resembling cholesterol clefts, were sometimes present within the areas of fibrosis. Chronic inflammation also included one or more small discrete focal clusters of alveoli containing small to moderate numbers of macrophages, occasionally mixed with a few neutrophils, and lined by hyperplastic epithelium. The extent, diversity, and intensity of the inflammatory alterations in the lungs of exposed rats were clearly distinguishable from those in the lungs of control rats.

Bronchial Lymph Node: Pigmentation in the bronchial lymph nodes similar to that in the lungs was observed in all exposure groups with the exception of 0.62 mg/m^3 males and females at 7 months (Tables 15, A5, and B5). As in the lung, the finely granular, black pigment in the bronchial lymph nodes was clearly related to nickel oxide exposure. Lymphoid hyperplasia was observed in the bronchial lymph nodes of 1.25 and 2.5 mg/m^3 males and females at 7 and 15 months, and the incidence at 2 years generally increased with exposure concentration. Lymphoid hyperplasia consisted of an increased number of cortical lymphocytes, often accompanied by enlargement of the lymph node. The lymphocytes were at different stages of differentiation and the overall architecture of the lymph node was maintained.

TABLE 15
Incidences of Nonneoplastic Lesions of the Bronchial Lymph Node in Rats in the 2-Year Inhalation Study of Nickel Oxide

	0 mg/m^3	0.62 mg/m^3	1.25 mg/m^3	2.5 mg/m^3
Male				
7-Month Interim Evaluation				
Lymph Node, Bronchial[a]	6	7	7	7
Hyperplasia, Lymphoid[b]	1 (1.0)[c]	0	7** (1.3)	4 (1.3)
Pigmentation	0	0	7** (1.0)	7** (1.0)
15-Month Interim Evaluation				
Lymph Node, Bronchial	5	5	5	5
Hyperplasia, Lymphoid	0	0	4* (1.3)	4* (1.0)
Pigmentation	0	5** (1.0)	5** (1.2)	5** (1.4)
2-Year Study				
Lymph Node, Bronchial	52	51	53	52
Hyperplasia, Lymphoid	0	7* (1.7)	10** (1.8)	18** (1.6)
Pigmentation	0	45** (1.4)	51** (1.8)	51** (1.8)
Female				
7-Month Interim Evaluation				
Lymph Node, Bronchial	6	7	7	6
Hyperplasia, Lymphoid	0	0	4* (1.0)	3 (1.0)
Pigmentation	0	0	7** (1.0)	6** (1.0)
15-Month Interim Evaluation				
Lymph Node, Bronchial	5	5	5	5
Hyperplasia, Lymphoid	0	0	3 (1.0)	3 (1.0)
Pigmentation	0	4* (1.0)	5** (1.4)	5** (1.4)
2-Year Study				
Lymph Node, Bronchial	49	50	53	52
Hyperplasia, Lymphoid	1 (4.0)	5 (1.6)	20** (1.5)	13** (1.7)
Pigmentation	0	43** (1.5)	52** (1.8)	47** (1.8)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (interim evaluations) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with lymph node examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Adrenal Medulla: At 2 years, there was an exposure-related increase in the incidence of benign pheochromocytoma in males and, more significantly, in females (Tables 16, A3, and B3). The incidence of bilateral benign pheochromocytoma in 2.5 mg/m^3 females was significantly greater than that of the controls. The incidence of all benign pheochromocytoma in 2.5 mg/m^3 females was significantly greater than that in the controls and exceeded the historical control range (Tables 16 and B4b). There was also an exposure-related increase in the incidence of benign or malignant pheochromocytoma (combined) in males. The incidence of benign or malignant pheochromocytoma (combined) in 2.5 mg/m^3 males was significantly greater than that of the controls, and the incidences in 1.25 and 2.5 mg/m^3 males exceeded the historical control range (Tables 16 and A4b). Benign pheochromocytomas are discrete clusters, sheets, or broad trabeculae of medullary cells (Plate 4). They range in size from those that merely compress adjacent tissue to those that expand to replace not only the adrenal medulla, but also the adrenal cortex, even to causing gross enlargement of the organ. Malignant pheochromocytomas invaded through the connective tissue capsule of the adrenal gland into surrounding tissue. The incidence of hyperplasia in 2.5 mg/m^3 females was significantly greater than that of the controls. Hyperplasias are irregular packets or clusters of medullary cells mildly altered in size, shape, and/or staining but which do not distort the adjacent parenchyma. Microscopically, focal medullary hyperplasia and pheochromocytoma form a morphologic continuum. Focal preneoplastic hyperplasia and pheochromocytoma were mutually exclusive diagnoses in the adrenal medulla. One or the other of these diagnoses occurred in most adrenal glands of exposed male rats.

Other Organs: There was an exposure-related decrease in the incidence of pituitary gland adenoma in males (24/53, 18/52, 16/52, 12/52; Table A3). There was an exposure-related increase in the incidence of interstitial cell adenoma in the testes of males (40/54, 46/53, 43/53, 47/52; Table A3). Very high incidences of pituitary gland neoplasms and testicular interstitial cell neoplasms occur spontaneously in F344/N rats in 2-year studies.

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Medulla in Rats in the 2-Year Inhalation Study of Nickel Oxide

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Male				
15-Month Interim Evaluation				
Adrenal Medulla[a]	5	5	5	5
Hyperplasia[b]	0	0	1 (2.0)[c]	2 (3.0)
Pheochromocytoma Benign	0	0	2	0
2-Year Study				
Adrenal Medulla	54	52	53	52
Hyperplasia	25 (2.2)	27 (2.1)	26 (2.6)	24 (2.5)
Pheochromocytoma Benign, Bilateral	10	11	9	16
Pheochromocytoma Benign (Includes Bilateral)				
Overall rate[d]	27/54 (50%)	24/52 (46%)	26/53 (49%)	32/52 (62%)
Adjusted rate[e]	81.8%	69.3%	83.1%	93.8%
Terminal rate[f]	9/14 (64%)	6/15 (40%)	10/15 (67%)	10/12 (83%)
First incidence (days)	475	570	519	553
Logistic regression test[g]	P=0.041	P=0.348N	P=0.561N	P=0.095
Pheochromocytoma Malignant				
Overall rate	0/54 (0%)	0/52 (0%)	1/53 (2%)	6/52 (12%)
Adjusted rate	0.0%	0.0%	2.8%	33.9%
Terminal rate	0/14 (0%)	0/15 (0%)	0/15 (0%)	3/12 (25%)
First incidence	—[h]	—	619	467
Logistic regression test	P<0.001	—	P=0.499	P=0.015
Pheochromocytoma Benign or Malignant[i]				
Overall rate	27/54 (50%)	24/52 (46%)	27/53 (51%)	35/52 (67%)
Adjusted rate	81.8%	69.3%	83.6%	97.0%
Terminal rate	9/14 (64%)	6/15 (40%)	10/15 (67%)	11/12 (92%)
First incidence	475	570	519	467
Logistic regression test	P=0.008	P=0.348N	P=0.521	P=0.027

(continued)

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Medulla in Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Female				
15-Month Interim Evaluation				
Adrenal Medulla	5	5	5	5
Hyperplasia	1 (1.0)	0	1 (1.0)	0
2-Year Study				
Adrenal Medulla	51	52	53	53
Hyperplasia	8 (1.3)	12 (2.3)	14 (2.3)	22** (2.5)
Pheochromocytoma Benign, Bilateral	1	0	1	5
Pheochromocytoma Benign (Includes Bilateral)[j]				
Overall rate	4/51 (8%)	7/52 (13%)	6/53 (11%)	18/53 (34%)
Adjusted rate	15.1%	21.1%	22.0%	56.5%
Terminal rate	2/21 (10%)	3/25 (12%)	2/20 (10%)	13/26 (50%)
First incidence	558	524	611	519
Logistic regression test	P<0.001	P=0.288	P=0.385	P=0.001

** Significantly different ($P \leq 0.01$) from the control group by the logistic regression test
[a] Number of animals with adrenal medulla examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[d] Number of animals with neoplasm per number of animals with adrenal medulla examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to the pairwise comparisons between the controls and that exposure group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposure group is indicated by N.
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence for 2-year NTP inhalation studies with untreated control groups (mean ± standard deviation): 176/623 (28.3% ± 12.0%); range 8%-50%. Feed studies: 400/1,182 (33.8% ± 10.9%); range 14%-63%
[j] Historical incidence for 2-year NTP inhalation studies: 35/608 (5.8% ± 4.9%); range 0%-14%. Feed studies: 49/1,175 (4.2% ± 2.5%); range 0%-8%

Tissue Burden Analyses

Nickel concentrations in the lung of exposed rats were significantly greater than those in the controls at 7 and 15 months, and nickel concentration increased with increasing exposure concentration and with time (Tables 17 and H4). At 7 and 15 months, the absolute lung weights of 1.25 and 2.5 mg/m^3 males and females in the lung burden groups were significantly greater than those of the controls; also, the absolute lung weight of 0.62 mg/m^3 females was greater than that of the controls at 7 months.

TABLE 17
Lung Weight and Lung Burden in Rats in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m^3	0.62 mg/m^3	1.25 mg/m^3	2.5 mg/m^3
Male				
n	6	7	7	7
7-Month Interim Evaluation				
Absolute lung wt (g)	1.72 ± 0.07	1.85 ± 0.07	2.43 ± 0.11**	2.59 ± 0.06**
μg Ni/lung	—[b]	326 ± 29.6**	930 ± 21.3**	1,817 ± 68.6**
μg Ni/g lung	—	175 ± 10.6**	388 ± 18.7**	701 ± 24.1**
μg Ni/g control lung	—	189 ± 17.2**	541 ± 12.4**	1,057 ± 39.9**
n	5	5	5	5
15-Month Interim Evaluation				
Absolute lung wt (g)	2.20 ± 0.04	2.15 ± 0.10	3.30 ± 0.16**	4.09 ± 0.12**
μg Ni/lung	—	696 ± 41.6**	2,439 ± 71.9**	4,573 ± 485.4**
μg Ni/g lung	—	328 ± 30.2**	746 ± 46.6**	1,116 ± 108.2**
μg Ni/g control lung	—	317 ± 18.9**	1,110 ± 32.7**	2,082 ± 221.1**
Female				
n	7	7	7	6
7-Month Interim Evaluation				
Absolute lung wt (g)	1.14 ± 0.03	1.31 ± 0.03*	1.65 ± 0.07**	1.78 ± 0.08**
μg Ni/lung	—	226 ± 13.3**	792 ± 86.5**	1,279 ± 132.2**
μg Ni/g lung	—	173 ± 10.1**	477 ± 44.4**	713 ± 45.2**
μg Ni/g control lung	—	198 ± 11.7**	694 ± 75.8**	1,122 ± 115.9**
n	5	5	5	5
15-Month Interim Evaluation				
Absolute lung wt (g)	1.56 ± 0.11	1.79 ± 0.10	2.41 ± 0.11**	3.02 ± 0.13**
μg Ni/lung	—	471 ± 42.5**	1,703 ± 140.5**	2,810 ± 389.1**
μg Ni/g lung	—	262 ± 14.8**	706 ± 41.8**	949 ± 146.4**
μg Ni/g control lung	—	302 ± 27.3**	1,093 ± 90.2**	1,804 ± 249.7**

* Significantly different ($P \leq 0.05$) from the control group by Williams' test (lung weight) or Shirley's test (lung burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error
[b] Results were below 0.540 μg Ni (the limit of detection) for 7-month males, 0.660 μg Ni for 7-month females, or 0.450 μg Ni for 15-month males and females, or below the level of quantitation.

MICE

16-DAY STUDY

One male mouse exposed to 5 mg/m^3 died on the last day of the study (Table 18); this death was not considered to be chemical related. Except for a slight body weight loss in 30 mg/m^3 males, final mean body weights and mean body weight gains of exposed male and female mice were similar to those of controls. No clinical findings in any group were related to nickel oxide exposure.

TABLE 18
Survival and Body Weights of Mice in the 16-Day Inhalation Study of Nickel Oxide

Dose (mg/m^3)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	22.6 ± 0.2	23.9 ± 0.8	1.3 ± 0.6	
1.2	5/5	23.6 ± 0.2	23.9 ± 0.5	0.3 ± 0.5	100
2.5	5/5	22.6 ± 0.4	23.8 ± 0.7	1.2 ± 0.7	100
5	4/5[c]	22.6 ± 0.5	23.3 ± 0.5	1.1 ± 0.4	98
10	5/5	22.6 ± 1.2	24.4 ± 0.8	1.8 ± 0.4	102
30	5/5	22.4 ± 0.5	22.3 ± 0.4	−0.1 ± 0.5	94
Female					
0	5/5	18.2 ± 0.4	20.2 ± 0.5	2.0 ± 0.6	
1.2	5/5	18.2 ± 0.2	20.2 ± 0.2	2.0 ± 0.3	100
2.5	5/5	18.4 ± 0.5	19.4 ± 0.6	1.0 ± 0.7	96
5	5/5	17.6 ± 0.5	20.2 ± 0.3	2.6 ± 0.3	100
10	5/5	17.2 ± 0.4	19.2 ± 0.3	2.0 ± 0.2	95
30	5/5	18.4 ± 0.2	19.3 ± 0.3	0.9 ± 0.1	95

[a] Number of animals surviving at 16 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. Differences from the control group were not significant by Dunnett's test.
[c] Day of death: 16

There were no chemical-related organ weight changes (Table F5). At necropsy, chemical-related gross lesions were limited to a slight enlargement of the bronchial lymph nodes in two males and two females exposed to 30 mg/m^3; in one male exposed to 30 mg/m^3, there was a solitary gray focus on the right intermediate lung lobe. Microscopically, the lymph node enlargement was attributed to lymphoid hyperplasia. Histopathologic changes were also present in the lungs (Table 19). In most mice exposed to 30 mg/m^3, there were inflammatory cell infiltrates in the pulmonary interstitium, primarily around blood vessels, and an increase in the number of alveolar macrophages in the lung. These inflammatory lesions were most prominent in the gray focus observed grossly in one male mouse. Pigment, consisting of densely stained, black particles, was present in the cytoplasm of alveolar macrophages as well as extracellularly within the alveolar spaces. At the lower exposure concentrations, histopathologic changes in the lungs were limited to accumulation of alveolar macrophages and the presence of pigment particles. No chemical-related histopathologic changes were observed in the lungs of mice exposed to 1.2 mg/m^3.

Concentrations of nickel in the lung increased with exposure concentration and were significantly greater than those of the controls in 1.2, 2.5, and 5 mg/m^3 males and females (Tables 20 and I1).

Because of the severity of lung lesions in mice exposed to 30 mg/m^3, 10 mg/m^3 was selected as the highest exposure concentration for the 13-week study.

TABLE 19
Incidences of Selected Nonneoplastic Lesions in Mice in the 16-Day Inhalation Study of Nickel Oxide

	0 mg/m^3	1.2 mg/m^3	2.5 mg/m^3	5 mg/m^3	10 mg/m^3	30 mg/m^3
Male						
Lung[a]	5	5	5	5	5	5
Alveolar Macrophage Hyperplasia[b]	0	0	0	0	5** (1.0)[c]	5** (2.6)
Interstitial Infiltrate	0	0	0	0	0	5** (2.8)
Pigment	0	0	4* (1.0)	5** (1.0)	5** (2.0)	5** (3.0)
Lymph Node, Bronchial	3	—[d]	—	—	3	4
Hyperplasia	0				0	2 (2.5)
Female						
Lung	5	5	5	5	5	5
Alveolar Macrophage Hyperplasia	0	0	0	0	3 (1.0)	5** (2.0)
Interstitial Infiltrate	1 (1.0)	0	0	1 (1.0)	0	4 (1.3)
Pigment	0	0	3 (1.0)	5** (1.0)	5** (1.8)	5** (2.2)
Lymph Node, Bronchial	2	—	—	—	3	4
Hyperplasia	0				0	2 (2.0)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[d] Tissue not examined at this exposure concentration

TABLE 20
Lung Weight and Lung Burden in Mice in the 16-Day Inhalation Study of Nickel Oxide[a]

	0 mg/m³	1.2 mg/m³	2.5 mg/m³	5 mg/m³
n	5	5	5	5
Male				
Absolute lung wt (g)	0.159 ± 0.005	0.154 ± 0.009	0.156 ± 0.003	0.156 ± 0.010
μg Ni/lung	—[b]	5 ± 0.1**	7 ± 0.5**	13 ± 0.7**
μg Ni/g lung	—	32 ± 2.4**	46 ± 3.6**	84 ± 7.8**
μg Ni/g control lung	—	31 ± 0.8**	45 ± 3.1**	81 ± 4.5**
Female				
Absolute lung wt (g)	0.149 ± 0.006	0.133 ± 0.004	0.141 ± 0.006	0.168 ± 0.006
μg Ni/lung	—	4 ± 0.2**	6 ± 0.4**	12 ± 0.8**
μg Ni/g lung	—	31 ± 2.1**	43 ± 0.9**	71 ± 5.7**
μg Ni/g control lung	—	27 ± 1.3**	41 ± 2.5**	80 ± 5.7**

** Significantly different ($P \leq 0.01$) from the control group by Dunnett's test (lung weight) or Shirley's test (lung burden parameters)
[a] Mean ± standard error
[b] Results were below 0.213 μg Ni (the limit of detection), or below the level of quantitation.

13-WEEK STUDY

One control female, three 1.2 mg/m^3 females, one 10 mg/m^3 male, and one 10 mg/m^3 female died during the study (Table 21). None of these deaths were considered to be related to nickel oxide exposure. Final mean body weights and mean body weight gains of exposed male and female mice were similar to those of the controls, and no clinical findings in any group were related to nickel oxide exposure.

In general, hematology differences in the mice (Table G3) were similar to those reported for rats at 13 weeks. The mice were less affected than the rats, and minimal differences occurred in fewer end points and exposure groups. Minimal lymphocytosis occurred, indicated by a lymphocyte count in 10 mg/m^3 males that was greater than that of the controls. Hematocrit values and erythrocyte counts in 5 and 10 mg/m^3 females and hemoglobin concentration in 5 mg/m^3 females were minimally greater than those of the controls.

No significant differences in sperm morphology or vaginal cytology between control and exposed mice were observed (Table J2).

TABLE 21
Survival and Body Weights of Mice in the 13-Week Inhalation Study of Nickel Oxide

Dose (mg/m^3)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	23.0 ± 0.9	32.4 ± 0.4	9.4 ± 0.7	
0.6	10/10	23.7 ± 0.3	32.6 ± 0.6	8.9 ± 0.5	101
1.2	10/10	23.5 ± 0.4	32.0 ± 0.3	8.5 ± 0.4	99
2.5	10/10	23.7 ± 0.5	31.4 ± 0.5	7.7 ± 0.6	97
5	10/10	22.5 ± 0.7	31.7 ± 0.9	9.2 ± 0.8	98
10	9/10[c]	23.4 ± 0.4	31.3 ± 0.6	7.7 ± 0.7	97
Female					
0	9/10[d]	19.8 ± 0.4	28.8 ± 0.5	9.0 ± 0.8	
0.6	10/10	19.9 ± 0.6	27.9 ± 0.6	8.0 ± 0.8	97
1.2	7/10[e]	19.5 ± 0.4	28.7 ± 1.0	9.4 ± 1.2	100
2.5	10/10	20.3 ± 0.5	27.6 ± 0.8	7.3 ± 0.5	96
5	10/10	19.6 ± 0.6	27.0 ± 0.7	7.4 ± 0.6	94
10	9/10[f]	20.3 ± 0.5	28.1 ± 0.5	7.9 ± 0.2	97

[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. Differences from the control group were not significant by Dunnett's test.
[c] Week of death: 4
[d] Week of death: 6
[e] Week of death: 2, 2, 2
[f] Week of death: 8

Absolute and relative lung weights of 10 mg/m^3 males and females and the relative lung weight of 5 mg/m^3 females were significantly greater than those of the controls (Table F6). Absolute and relative liver weights of 10 mg/m^3 males and relative liver weight of 5 mg/m^3 males were significantly less than those of the controls. At necropsy, chemical-related gross lesions were limited to a mild enlargement of the bronchial lymph nodes in four males and six females exposed to 10 mg/m^3. Three males and three females exposed to 5 mg/m^3 had similar gross lesions; enlarged lymph nodes were also observed in four 2.5 mg/m^3 females. Chemical-related histopathologic lesions were present in the lungs and bronchial lymph nodes (Table 22). Microscopically, the lymph node enlargement was usually attributed to lymphoid hyperplasia characterized by an increase in the number of lymphocytes, primarily in the paracortical areas of the lymph nodes. Lymphoid hyperplasia was present in mice exposed to 2.5, 5, or 10 mg/m^3. Densely stained, black pigment particles and aggregates of these pigment particles were present in the lymph nodes of 2.5, 5, and 10 mg/m^3 males and females. There were exposure- and chemical-related inflammatory lesions and pigment in the lungs of mice. At 0.6, 1.2, and 2.5 mg/m^3, there was a minimally detectable increase in the number of macrophages within the alveolar spaces. Pigment particles were present in the cytoplasm of alveolar macrophages as well as extracellularly within the alveolar spaces. At 5 and 10 mg/m^3, the severity and spectrum of inflammatory changes in the lung were slightly increased. Inflammatory lesions included interstitial infiltrates of primarily lymphocytes around blood vessels and chronic active inflammation characterized by a mild thickening of alveolar septa with a mixture of neutrophils and mononuclear inflammatory cells and a few fibroblasts. Granulomatous inflammation also occurred in a few mice exposed to 10 mg/m^3 and consisted of scattered, focal aggregates of large, epithelioid macrophages.

At the end of the 13-week study, nickel concentrations in the lung of 0.6, 2.5, and 10 mg/m^3 males were significantly greater than that in the controls, and absolute lung weight of these 10 mg/m^3 males was significantly greater than that of the controls (Tables 23 and I2).

TABLE 22
Incidences of Selected Nonneoplastic Lesions in Mice in the 13-Week Inhalation Study of Nickel Oxide

	0 mg/m³	0.6 mg/m³	1.2 mg/m³	2.5 mg/m³	5 mg/m³	10 mg/m³
Male						
Lung[a]	10	10	10	10	10	9
Alveolar Macrophage Hyperplasia[b]	0	10** (1.0)[c]	10** (1.0)	10** (1.0)	10** (1.0)	9** (1.1)
Inflammation, Chronic Active	0	0	0	0	0	3 (1.0)
Inflammation, Granulomatous	0	0	0	0	0	3 (1.0)
Perivascular Lymphocytic Infiltrate	0	0	0	1 (1.0)	3 (1.0)	8** (1.0)
Pigment	0	10** (1.0)	10** (1.0)	10** (1.0)	10** (1.0)	9** (1.0)
Lymph Node, Bronchial	7	10	6	8	6	7
Hyperplasia	0	0	0	1 (1.0)	3 (1.0)	5** (1.3)
Pigment	0	0	0	5* (1.0)	5** (1.0)	6** (1.0)
Female						
Lung	9	10	7	10	10	9
Alveolar Macrophage Hyperplasia	0	10** (1.0)	7** (1.0)	10** (1.0)	10** (1.1)	9** (1.0)
Inflammation, Chronic Active	0	0	0	0	1 (1.0)	3 (1.1)
Inflammation, Granulomatous	0	0	0	0	0	1 (1.0)
Perivascular Lymphocytic Infiltrate	0	1 (1.0)	0	4 (1.0)	6** (1.1)	8** (1.1)
Pigment	0	10** (1.0)	7** (1.0)	10** (1.0)	10** (1.0)	9** (1.0)
Lymph Node, Bronchial	8	9	4	10	10	9
Hyperplasia	0	0	0	4 (1.0)	3 (1.0)	7** (1.3)
Pigment	0	0	0	8** (1.0)	8** (1.0)	8** (1.0)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

TABLE 23
Lung Weight and Lung Burden in Male Mice in the 13-Week Inhalation Study of Nickel Oxide[a]

	0 mg/m³	0.6 mg/m³	2.5 mg/m³	10 mg/m³
Male				
n	6	5	6	5
Absolute lung weight (g)	0.176 ± 0.012	0.179 ± 0.004	0.179 ± 0.014	0.244 ± 0.019**
μg Ni/lung	—[b]	7 ± 0.6**	36 ± 3.3**	171 ± 15.5**
μg Ni/g lung	—	42 ± 2.9**	202 ± 18.3**	736 ± 123.0**
μg Ni/g control lung	—	42 ± 3.4**	204 ± 18.9**	973 ± 88.0**

** Significantly different ($P \leq 0.01$) from the control group by Dunnett's test (lung weight) or Shirley's test (lung burden parameters)
[a] Mean ± standard error
[b] Results were below 0.255 μg Ni (the limit of detection), or below the level of quantitation.

Dose Selection Rationale: Based on the wider spectrum of inflammatory lesions in the lung and increased lung weights in 10 mg/m³ male and female mice in the 13-week study, nickel oxide exposure concentrations selected for the 2-year inhalation study in mice were 1.25, 2.5, and 5 mg/m³.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 24 and in the Kaplan-Meier survival curves in Figure 4. Survival of exposed male and female mice was similar to that of the controls.

Body Weights and Clinical Findings

Mean body weights of exposed males and of females exposed to 1.25 or 2.5 mg/m^3 were similar to those of the controls throughout most of the study (Tables 25 and 26 and Figure 5). Mean body weights of females exposed to 5 mg/m^3 were less than those of the controls during the second year of the study. No chemical-related clinical findings were observed in male or female mice during the 2-year study.

Hematology

No chemical-related differences in hematology parameters were observed in male or female mice at the 15-month interim evaluation (Table G4).

TABLE 24
Survival of Mice in the 2-Year Inhalation Study of Nickel Oxide

	0 mg/m^3	1.25 mg/m^3	2.5 mg/m^3	5 mg/m^3
Male				
Animals initially in study	78	77	76	79
7-Month interim evaluation[a]	5	5	5	5
15-Month interim evaluation[a]	5	5	5	5
Accidental deaths[a]	10	0	0	0
Missexed[a]	1	0	0	0
Moribund	23	26	26	29
Natural deaths	15	18	11	17
Animals surviving to study termination	19	23	29	23
Percent probability of survival at end of study[b]	33	34	44	33
Mean survival (days)[c]	526	605	649	612
Survival analysis[d]	P=0.830N	P=0.942N	P=0.188N	P=0.931N
Female				
Animals initially in study	74	76	74	75
7-Month interim evaluation[a]	5	5	5	5
15-Month interim evaluation[a]	5	5	5	5
Accidental deaths[a]	1	0	1	0
Pregnant/Missexed[a]	0	0	1	1
Moribund	15	18	9	16
Natural deaths	7	8	11	10
Animals surviving to study termination	41[e]	40[f]	42	38
Percent probability of survival at end of study	65	61	68	59
Mean survival (days)	621	665	640	662
Survival analysis	P=0.763	P=0.854	P=0.877N	P=0.735

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on the first day of terminal sacrifice
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed columns. A negative trend or a lower mortality in an exposure group is indicated by N.
[e] Includes one animal that died during the last week of the study.
[f] Includes two animals that died during the last week of the study.

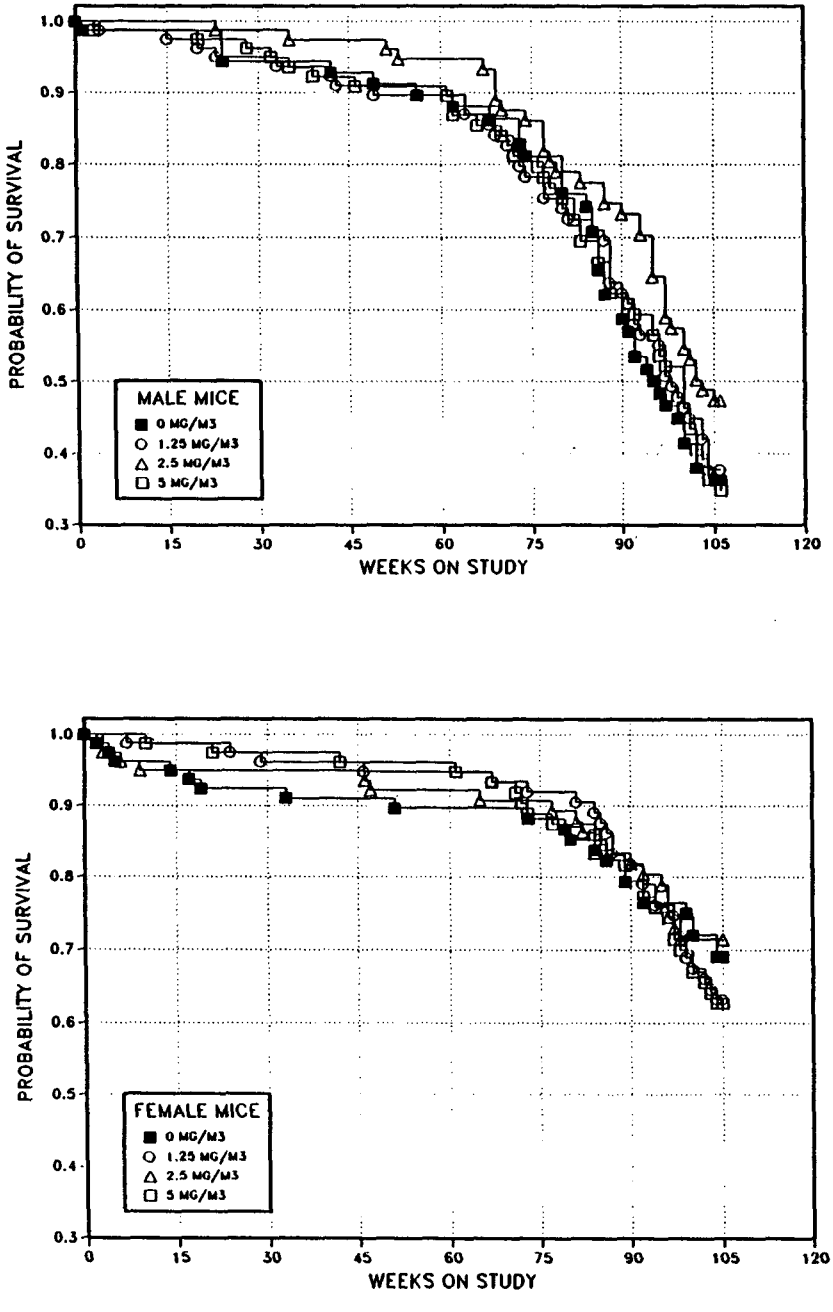

FIGURE 4
Kaplan-Meier Survival Curves for Mice Administered Nickel Oxide by Inhalation for 2 Years

TABLE 25
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Nickel Oxide[a]

Weeks on Study	0 mg/m3 Av. Wt. (g)	0 mg/m3 No. of Survivors	1.25 mg/m³ Av. Wt. (g)	1.25 mg/m³ Wt. (% of controls)	1.25 mg/m³ No. of Survivors	2.5 mg/m³ Av. Wt. (g)	2.5 mg/m³ Wt. (% of controls)	2.5 mg/m³ No. of Survivors	5 mg/m³ Av. Wt. (g)	5 mg/m³ Wt. (% of controls)	5 mg/m³ No. of Survivors
1	23.8	79	23.6	99	80	23.4	98	80	23.4	98	80
2	25.9	78	26.0	100	80	26.0	100	80	25.7	99	80
3	27.4	78	27.6	101	80	27.4	100	80	27.4	100	80
4	27.7	78	28.0	101	79	27.8	100	80	28.2	102	79
5	28.1	78	28.2	100	79	28.3	101	80	28.7	102	79
6	29.9	78	29.6	99	79	29.7	99	80	30.1	101	79
7	30.7	78	30.2	98	79	30.0	98	80	30.6	100	79
8	30.5	78	30.4	100	79	30.4	100	80	30.7	101	79
10	31.2	78	31.0	99	79	30.9	99	80	31.3	100	79
11	31.9	68	30.9	97	79	31.4	98	80	31.9	100	79
12	31.6	68	31.1	98	79	31.3	99	80	31.9	101	79
13	32.2	68	31.9	99	79	31.6	98	80	32.7	102	79
17	33.5	68	33.3	99	78	33.4	100	80	34.0	102	79
21	34.8	68	34.6	99	77	34.5	99	80	35.3	101	78
25	36.1	65	35.5	98	76	35.6	99	79	35.9	99	78
29[b]	36.5	60	35.7	98	71	35.9	98	74	36.9	101	72
33	37.4	60	37.0	99	70	37.3	100	74	38.0	102	71
37	38.7	60	37.7	97	70	38.0	98	73	38.3	99	70
41	39.2	60	38.2	97	70	38.4	98	73	39.1	100	69
45	39.0	59	38.4	99	68	38.6	99	73	39.5	101	69
49	40.0	58	39.1	98	67	39.2	98	73	40.0	100	68
53	40.9	58	39.8	97	67	40.5	99	71	40.9	100	68
57	41.4	57	40.5	98	67	40.7	98	71	40.9	99	68
61	41.4	57	41.0	99	67	41.8	101	71	41.8	101	67
65	42.2	56	41.0	97	65	41.9	99	71	41.7	99	65
69[b]	42.6	50	41.6	98	58	41.4	97	62	41.9	98	59
73	42.4	49	40.5	96	55	41.4	98	61	41.6	98	56
77	42.0	47	40.2	96	54	40.9	97	60	41.0	98	55
81	42.2	44	39.5	94	51	40.9	97	55	40.6	96	52
85	41.7	41	39.5	95	49	40.8	98	54	40.4	97	48
89	42.3	36	39.2	93	44	40.2	95	52	40.1	95	43
93	41.6	31	38.5	93	39	39.4	95	49	38.7	93	41
97	41.4	27	38.0	92	35	38.8	94	42	38.9	94	36
101	41.2	24	38.2	93	31	38.2	93	37	38.2	93	30
Mean for weeks											
1-13	29.2		29.0	99		29.0	99		29.4	101	
14-52	37.2		36.6	98		36.8	99		37.4	101	
53-101	41.8		39.8	95		40.5	97		40.5	97	

[a] A few animals in each exposure group were used only in special studies.
[b] Interim evaluations occurred during weeks 29 and 66.

TABLE 26
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Nickel Oxide[a]

Weeks on Study	0 mg/m3 Av. Wt. (g)	0 mg/m3 No. of Survivors	1.25 mg/m³ Av. Wt. (g)	1.25 mg/m³ Wt. (% of controls)	1.25 mg/m³ No. of Survivors	2.5 mg/m³ Av. Wt. (g)	2.5 mg/m³ Wt. (% of controls)	2.5 mg/m³ No. of Survivors	5 mg/m³ Av. Wt. (g)	5 mg/m³ Wt. (% of controls)	5 mg/m³ No. of Survivors
1	19.3	80	19.5	101	80	19.0	98	80	18.9	98	80
2	21.2	79	21.8	103	80	21.0	99	80	21.1	100	80
3	22.3	78	23.1	104	80	22.7	102	78	22.8	102	80
4	22.3	77	23.7	106	80	23.3	105	78	23.6	106	80
5	23.3	76	24.0	103	80	23.6	101	78	23.8	102	80
6	25.3	76	25.6	101	80	25.2	100	77	25.4	100	80
7	26.1	76	26.1	100	79	25.7	99	77	26.1	100	80
8	26.2	76	26.5	101	79	25.9	99	77	25.5	97	80
10	26.7	76	27.1	102	79	26.1	98	75	26.6	100	80
11	27.4	76	26.9	98	79	26.8	98	75	27.4	100	79
12	27.3	76	26.9	99	79	26.8	98	75	27.2	100	79
13	27.8	76	27.8	100	79	27.3	98	75	27.9	100	79
17	29.4	74	29.9	102	79	28.9	98	75	29.3	100	79
21	30.3	73	31.1	103	79	30.4	100	75	30.9	102	78
25	31.6	73	32.0	101	78	31.7	100	75	31.6	100	78
29[b]	33.0	68	33.0	100	73	31.9	97	70	32.3	98	73
33	34.6	67	34.1	99	72	33.8	98	70	33.7	97	73
37	35.7	67	35.2	99	72	34.2	96	70	34.6	97	73
41	36.5	67	35.7	98	72	34.8	95	70	35.6	98	73
45	36.7	67	36.2	99	72	35.6	97	70	36.4	100	72
49	37.7	67	37.5	100	71	36.5	97	67	36.6	97	72
53	39.0	66	38.6	99	71	38.0	97	67	37.5	96	72
57	39.4	66	39.1	99	71	37.9	96	67	37.0	94	72
61	39.7	66	39.7	100	71	38.6	97	67	38.0	96	71
65	40.6	66	39.8	98	71	39.5	97	66	38.0	94	71
69[b]	41.4	61	40.8	99	65	39.0	94	61	39.4	95	65
73	40.7	61	39.6	97	65	38.9	96	61	38.9	96	62
77	40.5	60	39.3	97	64	38.8	96	60	38.5	95	61
81	40.3	58	38.1	95	63	38.3	95	60	37.5	93	61
85	39.3	57	37.8	96	61	38.1	97	56	36.8	94	60
89	39.3	54	37.7	96	58	38.1	97	56	35.3	90	56
93	39.2	52	37.2	95	55	37.2	95	54	34.6	88	53
97	38.2	52	36.4	95	52	36.6	96	49	35.5	93	49
101	38.3	49	36.7	96	47	36.0	94	48	34.5	90	46
Mean for weeks											
1-13	24.6		24.9	101		24.5	100		24.7	100	
14-52	33.9		33.9	100		33.1	98		33.4	99	
53-101	39.7		38.5	97		38.1	96		37.0	93	

[a] A few animals in each exposure group were used only in special studies.
[b] Interim evaluations occurred during weeks 29 and 66.

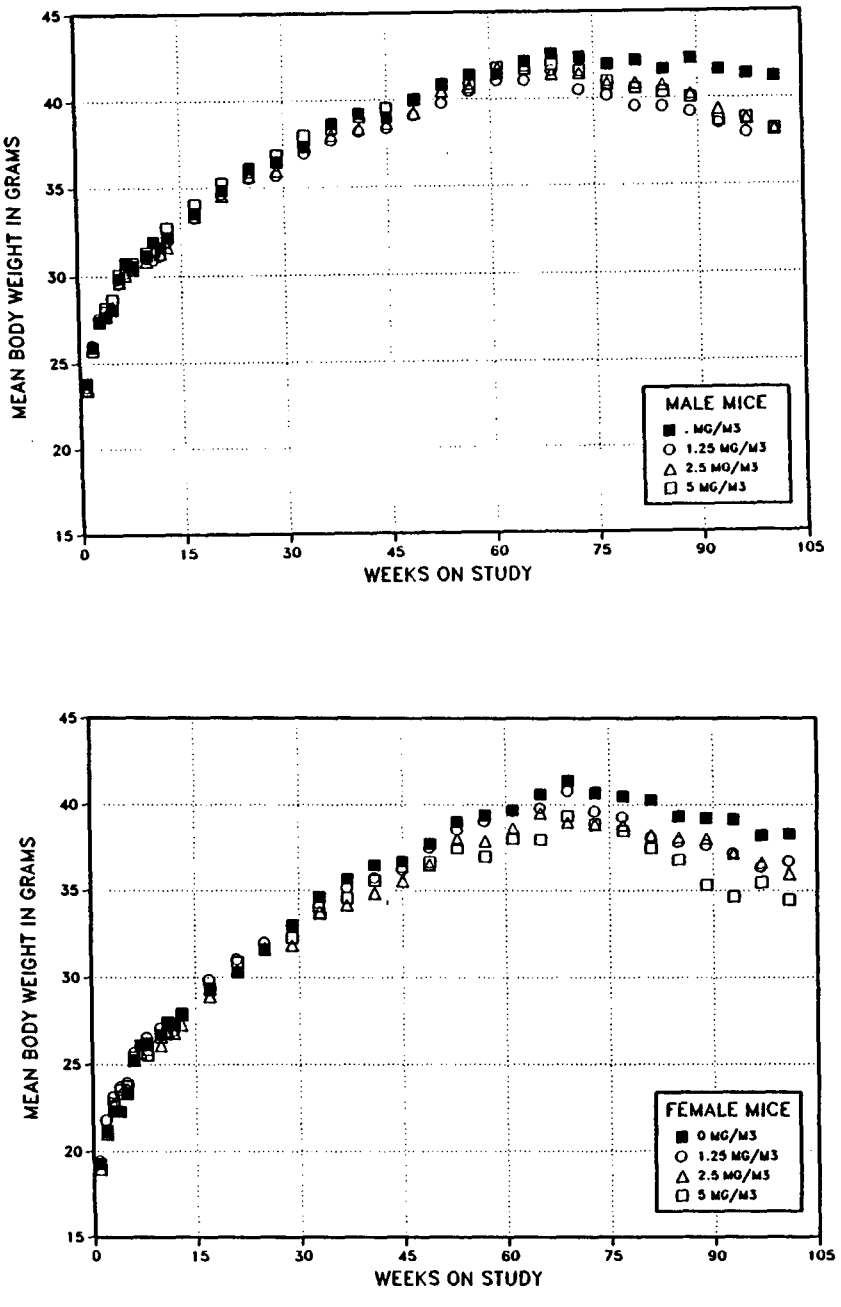

FIGURE 5
Growth Curves for Mice Administered Nickel Oxide by Inhalation for 2 Years

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of nonneoplastic lesions of the lung, lymph nodes, and urogenital tract and neoplasms of the lung, liver, and harderian gland. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Lung: At the 7-month interim evaluation, absolute and relative lung weights of males exposed to 2.5 or 5 mg/m^3 were significantly greater than those of the controls (Table F7). At 15 months, absolute and relative lung weights of 5 mg/m^3 males and females were significantly greater than those of the controls (Table F8). At 2 years, the incidence of alveolar/bronchiolar adenoma in 2.5 mg/m^3 females was significantly greater than that of the controls, as was the incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in 1.25 mg/m^3 females (Tables 27 and D3). The incidences of these neoplasms in these groups exceeded the historical control ranges from NTP inhalation studies (Tables 27 and D4). Alveolar/bronchiolar adenomas were typically discrete proliferations of alveolar and papillary structures lined by a single layer of large cuboidal epithelial cells that compressed the adjacent lung parenchyma. Alveolar/bronchiolar carcinomas were either discrete or invasive and consisted of alveolar, papillary, or tubular structures composed of densely packed atypical epithelial cells usually forming multiple layers or solid clusters. Morphologically, alveolar/bronchiolar neoplasms were typical of spontaneously occurring neoplasms in B6C3F$_1$ mice.

Generally, incidences of chronic inflammation increased with increasing exposure concentration in males and females at 7 and 15 months (Tables 27, C5, and D5). Bronchialization of minimal severity in exposed animals and proteinosis were first observed at 15 months. At 2 years, the incidences of chronic inflammation, bronchialization, and proteinosis in exposed groups of males and females were significantly greater than those of the controls. The severity of chronic inflammation increased with increasing exposure concentration in females, and proteinosis was most severe in 5 mg/m^3 males and females. Chronic inflammation included small to moderate numbers of mononuclear inflammatory cells (principally lymphocytes, with fewer macrophages) around the vessels and airways; variable numbers of macrophages within alveolar spaces, often obscured by particulate pigment; and occasional focal aggregates of macrophages mixed with lymphocytes, or rarely neutrophils, within alveolar lumens. Occasionally, long, thin, brightly eosinophilic crystalline material within alveolar lumens or airways was observed either free or within macrophages (Plate 5). These crystalline structures also occurred in a few control mice and were associated with inflammation around pulmonary neoplasms. Bronchialization consisted of hyperplastic and/or hypertrophic cuboidal epithelial cells extending from terminal bronchioles into alveolar ducts and adjacent proximal alveoli of nickel oxide exposed mice (Plate 6). Because these cuboidal cells were not observed to have cilia and no attempts were made to determine their cell of origin, the term bronchialization in this study corresponds to the overall light microscopic appearance only. Proteinosis was an accumulation of varying amounts of eosinophilic granular to hyaline material, usually containing pigment particles, within alveolar lumens.

Pigment occurred in the lungs of nearly all exposed mice at 7 and 15 months and at 2 years, and the severity increased with increasing exposure concentration (Tables 27, C5, and D5). Pigmentation of the lung consisted of fine, black, slightly refractile particles, either within alveolar macrophages or adherent to proteinaceous material in the alveolar spaces (Plate 7). Exposure-related pigment in the lung was distinguishable from the spontaneously occurring endogenous pigment hemosiderin. Occasionally, pigmented macrophages were observed in the interstitium or lymphoid tissue around airways.

Focal alveolar hyperplasia in the lungs secondary to an inflammatory reaction was not separately diagnosed. Focal alveolar epithelial hyperplasia, part of the morphologic continuum toward neoplasia, was occasionally observed. Focal alveolar hyperplasia consisted of clusters of alveoli lined by a single layer of typical type II cuboidal epithelial cells maintaining normal alveolar architecture.

TABLE 27
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Inhalation Study of Nickel Oxide

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
Male				
7-Month Interim Evaluation				
Lung[a]	5	5	5	5
Inflammation, Chronic[b]	0	2 (1.0)[c]	3 (1.0)	3 (1.0)
Alveolus, Pigmentation	0	5** (1.0)	5** (1.0)	5** (1.2)
Alveolar/bronchiolar Adenoma	1	0	0	0
15-Month Interim Evaluation				
Lung	5	5	5	5
Inflammation, Chronic	1 (1.0)	0	2 (1.0)	4 (1.8)
Bronchialization	0	1 (1.0)	0	2 (1.0)
Alveolar Epithelium, Hyperplasia, Focal	1 (3.0)	0	0	0
Alveolus, Pigmentation	0	5** (1.2)	5** (1.4)	5** (2.2)
Alveolus, Proteinosis	0	0	1 (1.0)	3 (1.0)
Alveolar/bronchiolar Adenoma	1	0	0	0
2-Year Study				
Lung	57	67	66	69
Fibrosis	0	0	0	1 (1.0)
Inflammation, Chronic	0	21** (1.4)	34** (1.4)	55** (1.4)
Bronchialization	0	24** (1.0)	40** (1.0)	40** (1.0)
Alveolar Epithelium, Hyperplasia, Focal	1 (4.0)	1 (2.0)	2 (3.0)	0
Alveolus, Pigmentation	0	65** (1.1)	66** (1.7)	68** (2.1)
Alveolus, Proteinosis	0	12** (1.2)	22** (1.5)	43** (1.8)
Alveolar/bronchiolar Adenoma	7	5	6	11
Alveolar/bronchiolar Carcinoma, Multiple	0	1	0	1
Alveolar/bronchiolar Carcinoma (Single or Multiple)	4	10	9	6
Alveolar/bronchiolar Adenoma or Carcinoma[d]				
Overall rate[e]	9/57 (16%)	14/67 (21%)	15/66 (23%)	14/69 (20%)
Adjusted rate[f]	36.3%	41.4%	43.6%	39.7%
Terminal rate[g]	5/19 (26%)	6/23 (26%)	11/29 (38%)	6/23 (26%)
First incidence (days)	559	512	483	489
Logistic regression test[h]	P=0.393	P=0.322	P=0.380	P=0.364
Female				
7-Month Interim Evaluation				
Lung	5	5	5	5
Inflammation, Chronic	0	1 (2.0)	4* (1.0)	4* (1.3)
Alveolus, Pigmentation	0	4* (1.0)	5** (1.2)	5** (1.2)

(continued)

TABLE 27
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
Female (continued)				
15-Month Interim Evaluation				
Lung	5	5	5	5
Inflammation, Chronic	0	2 (1.5)	4* (1.0)	4* (1.3)
Bronchialization	0	0	3 (1.0)	3 (1.0)
Alveolus, Pigmentation	0	4* (1.0)	5** (1.4)	5** (2.0)
Alveolus, Proteinosis	0	0	0	3 (1.3)
Alveolar/bronchiolar Adenoma	0	0	1	0
2-Year Study				
Lung	64	66	63	64
Fibrosis	0	0	1 (2.0)	3 (1.0)
Inflammation, Chronic	7 (1.4)	43** (1.4)	53** (1.6)	52** (1.9)
Inflammation, Chronic Active	0	0	1 (2.0)	0
Bronchialization	0	35** (1.0)	39** (1.0)	40** (1.0)
Alveolar Epithelium, Hyperplasia, Focal	0	0	1 (2.0)	0
Alveolus, Pigmentation	0	64** (1.3)	61** (1.9)	64** (2.4)
Alveolus, Proteinosis	0	8** (1.5)	17** (1.3)	29** (1.7)
Alveolar/bronchiolar Adenoma, Multiple	0	2	0	0
Alveolar/bronchiolar Adenoma (Single and Multiple)	2	4	10*	3
Alveolar/bronchiolar Carcinoma, Multiple	0	1	0	0
Alveolar/bronchiolar Carcinoma (Single and Multiple)	4	11	4	5
Alveolar/bronchiolar Adenoma or Carcinoma[i]				
Overall rate	6/64 (9%)	15/66 (23%)	12/63 (19%)	8/64 (13%)
Adjusted rate	13.8%	30.8%	25.7%	17.4%
Terminal rate	4/41 (10%)	8/40 (20%)	8/42 (19%)	4/38 (11%)
First incidence (days)	694	583	630	469
Logistic regression test	P=0.487N	P=0.043	P=0.099	P=0.422

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (interim evaluations) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with lung examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[d] Historical incidence for 2-year NTP inhalation studies with untreated control groups (mean ± standard deviation): 205/952 (21.5% ± 8.0%); range 10%-42%. Feed studies: 249/1,319 (18.9% ± 7.6%); range 4%-32%
[e] Number of animals with neoplasm per number of animals with lung examined microscopically
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[g] Observed incidence in animals surviving until the end of the study
[h] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to the pairwise comparisons between the controls and that exposure group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by N.
[i] Historical incidence for 2-year NTP inhalation studies: 97/944 (10.3% ± 3.7%); range 0%-16%. Feed studies: 102/1,319 (7.7% ± 5.3%); range 2%-26%

Bronchial Lymph Node: Lymphoid hyperplasia occurred in one 2.5 mg/m^3 male and one 1.25 mg/m^3 female at 7 months (Tables 28, C5, and D5). At 15 months, lymphoid hyperplasia occurred in males exposed to 2.5 and 5 mg/m^3 and in all exposed groups of females. At 2 years, lymphoid hyperplasia occurred in some control animals, but this lesion was still observed more often in exposed males and females and the incidence increased with exposure concentration. Pigmentation was observed in the bronchial lymph nodes of exposed males and females at 7 and 15 months. Pigmentation was also observed in nearly all exposed animals at 2 years (Plate 8). Pigmentation was not observed in the bronchial lymph nodes of control males or females at any time. The severity of these lesions appeared to be unaffected by exposure concentration.

Lymphoid hyperplasia was characterized by an increase in cortical or paracortical lymphocytes resulting in a mild to moderate increase in lymph node size. The lymphocytes were at different stages of differentiation, and the overall architecture of the lymph node was maintained. Pigmentation consisted of variable numbers of discrete aggregates of fine, black, granular material, apparently within macrophages, located predominantly within the medullary area. The pigment resembled that observed in the lung and was clearly related to nickel oxide exposure.

Liver: At 2 years, the incidence of hepatocellular carcinoma in 1.25 mg/m^3 males was significantly greater than that of the controls (6/57, 16/67, 11/66, 15/69; Table C3). However, the incidence was within the historical control range (Table C4b) and the incidence of adenoma or carcinoma (combined) was not significantly greater than that of the controls (12/57, 20/67, 23/66, 20/69).

TABLE 28
Incidences of Nonneoplastic Lesions of the Bronchial Lymph Node in Mice in the 2-Year Inhalation Study of Nickel Oxide

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
Male				
7-Month Interim Evaluation				
Lymph Node, Bronchial[a]	4	3	5	4
Hyperplasia, Lymphoid[b]	0	0	1 (1.0)[c]	0
Pigmentation	0	2 (1.0)	5** (1.0)	4* (1.0)
15-Month Interim Evaluation				
Lymph Node, Bronchial	5	5	5	5
Hyperplasia, Lymphoid	0	0	2 (1.5)	4* (2.3)
Pigmentation	0	4* (1.3)	5** (1.6)	5** (1.2)
2-Year Study				
Lymph Node, Bronchial	45	56	61	62
Hyperplasia, Lymphoid	5 (2.0)	18* (1.8)	28** (2.0)	33** (1.8)
Pigmentation	0	55** (1.5)	61** (1.9)	60** (2.1)
Female				
7-Month Interim Evaluation				
Lymph Node, Bronchial	3	4	5	5
Pigmentation	0	1 (1.0)	5** (1.0)	5** (1.0)
15-Month Interim Evaluation				
Lymph Node, Bronchial	5	5	5	5
Hyperplasia, Lymphoid	0	3 (1.3)	4* (1.0)	4* (1.0)
Pigmentation	0	4* (1.0)	5** (1.6)	5** (1.4)
2-Year Study				
Lymph Node, Bronchial	54	63	59	62
Hyperplasia, Lymphoid	14 (1.8)	37** (2.0)	40** (1.9)	44** (2.2)
Pigmentation	0	58** (1.5)	56** (1.8)	60** (2.0)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (interim evaluations) or the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with bronchial lymph node examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Tissue Burden Analyses

Nickel concentrations in the lungs of exposed mice were significantly greater than those in the controls at 7 and 15 months, and nickel concentration increased with increasing exposure concentration and with time (Tables 29 and I3). In lung burden analysis groups, absolute lung weight of 2.5 and 5 mg/m^3 males at 7 and 15 months and of 5 mg/m^3 females at 15 months were significantly greater than those of the controls.

TABLE 29
Lung Weight and Lung Burden in Mice in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m^3	1.25 mg/m^3	2.5 mg/m^3	5 mg/m^3
n	5	5	5	5
Male				
7-Month Interim Evaluation				
Absolute lung weight (g)	0.192 ± 0.009	0.208 ± 0.004	0.240 ± 0.010**	0.238 ± 0.006**
μg Ni/lung	—[b]	34 ± 2.1**	107 ± 12.0**	246 ± 11.2**
μg Ni/g lung	—	162 ± 9.6**	442 ± 37.1**	1,034 ± 33.1**
μg Ni/g control lung	—	176 ± 11.0**	556 ± 62.3**	1,283 ± 58.1**
15-Month Interim Evaluation				
Absolute lung weight (g)	0.234 ± 0.017	0.246 ± 0.021	0.306 ± 0.020*	0.382 ± 0.019**
μg Ni/lung	—	80 ± 5.1**	296 ± 35.5**	696 ± 81.9**
μg Ni/g lung	—	331 ± 30.3**	959 ± 67.1**	1,798 ± 134.5**
μg Ni/g control lung	—	340 ± 21.8**	1,265 ± 151.5**	2,973 ± 349.9**
Female				
7-Month Interim Evaluation				
Absolute lung weight (g)	0.178 ± 0.010	0.206 ± 0.011	0.228 ± 0.019	0.232 ± 0.022
μg Ni/lung	—	35 ± 1.6**	120 ± 8.1**	196 ± 15.3**
μg Ni/g lung	—	169 ± 6.0**	533 ± 36.4**	861 ± 70.1**
μg Ni/g control lung	—	195 ± 9.1**	674 ± 45.2**	1,101 ± 86.2**
15-Month Interim Evaluation				
Absolute lung weight (g)	0.248 ± 0.010	0.264 ± 0.010	0.294 ± 0.018	0.340 ± 0.026**
μg Ni/lung	—	119 ± 10.1**	365 ± 39.9**	771 ± 111.9**
μg Ni/g lung	—	451 ± 31.4**	1,237 ± 102.6**	2,258 ± 265.1**
μg Ni/g control lung	—	481 ± 40.9**	1,472 ± 160.9**	3,108 ± 451.3**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test (lung weight) or Shirley's test (lung burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error
[b] Results were below 0.400 μg Ni (the limit of detection) for 7-month mice or 0.352 μg Ni for 15-month mice, or below the level of quantitation.

GENETIC TOXICOLOGY

Nickel oxide was tested for induction of micronuclei in normochromatic erythrocytes of male and female mice exposed by inhalation for 13 weeks. The compound did not induce an increase in the frequency of micronucleated normochromatic erythrocytes in peripheral blood samples (Table E1).

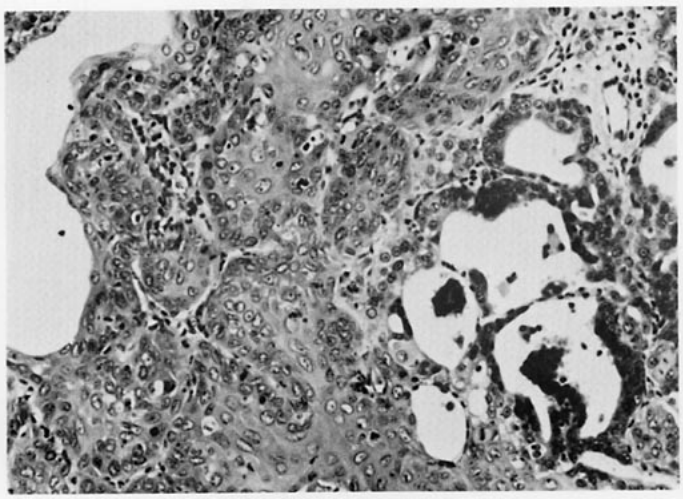

PLATE 1
Lung of a male F344/N rat exposed to 1.25 mg nickel oxide/m^3 by inhalation for 2 years. Squamous differentiation within an alveolar/bronchiolar carcinoma. H&E; 105×

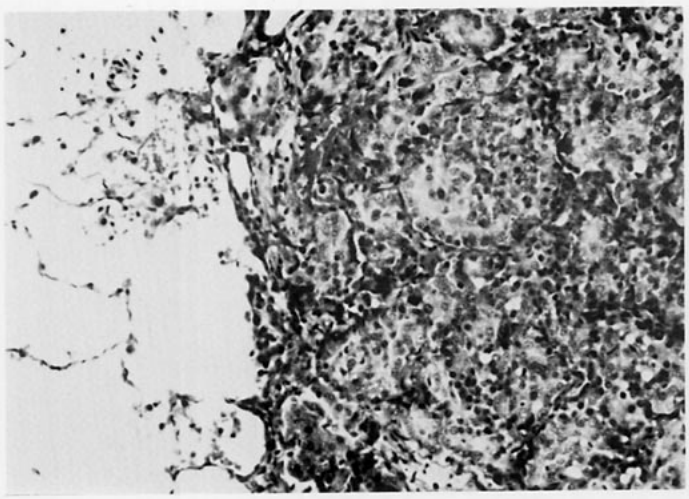

PLATE 2
Alveolar/bronchiolar adenoma in the lung of a female F344/N rat exposed to 2.5 mg nickel oxide/m^3 by inhalation for 2 years. The clusters of neoplastic cells fill alveolar spaces and make a mass well demarcated from the surrounding alveoli. H&E; 135×

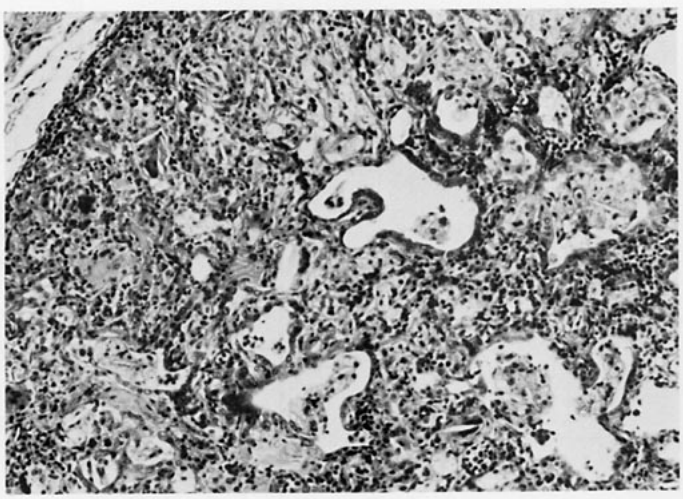

PLATE 3
Subpleural focus of marked chronic inflammation in the lung of a male F344/N rat exposed to 2.5 mg nickel oxide/m^3 by inhalation for 2 years. Note alveolar spaces filled with macrophages and other inflammatory cells, protein, and cell debris; alveolar septa thickened by inflammatory cell infiltrates and increased connective tissue; and prominent cuboidal epithelium lining air spaces. H&E; 105×

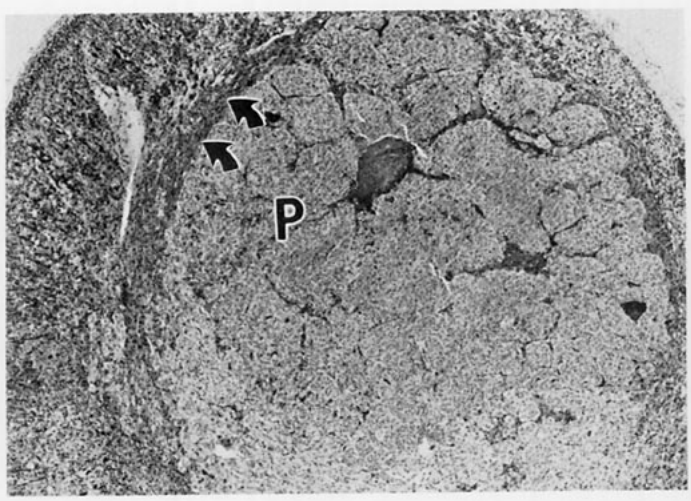

PLATE 4
Benign pheochromocytoma (P) in the medulla of the adrenal gland of a female F344/N rat exposed to 2.5 mg nickel oxide/m^3 by inhalation for 2 years. Note compression (arrows) of the adrenal cortex. H&E; 35×

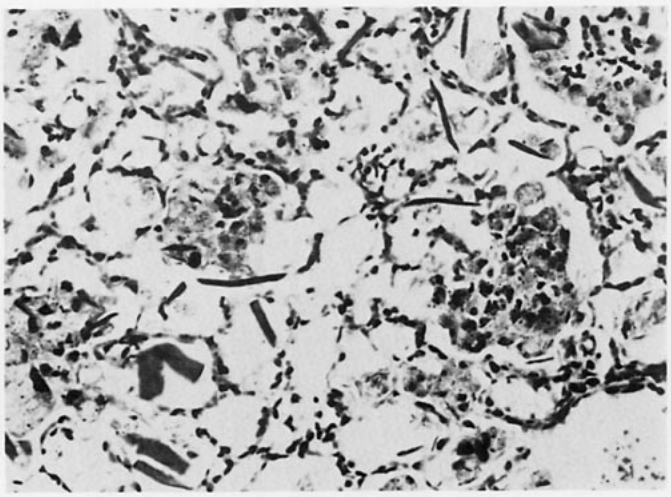

PLATE 5
Focus of marked inflammation in the lung of a female B6C3F$_1$ mouse exposed to 5 mg nickel oxide/m^3 by inhalation for 2 years. Note protein, macrophages, crystalline rods, and particulate pigment within alveolar spaces. H&E; 65×

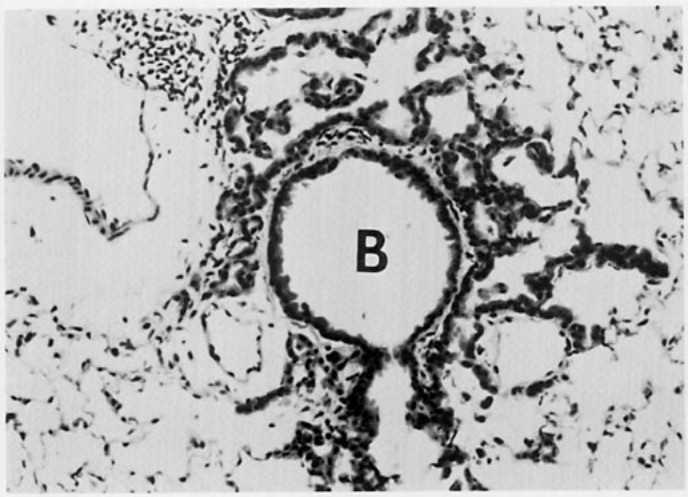

PLATE 6
Bronchialization (alveolar epithelial hyperplasia) in the lung of a male B6C3F$_1$ mouse exposed to 2.5 mg nickel oxide/m^3 by inhalation for 2 years. Note cuboidal cells extending from the terminal bronchiole (B) onto the septa of adjacent alveoli. H&E; 135×

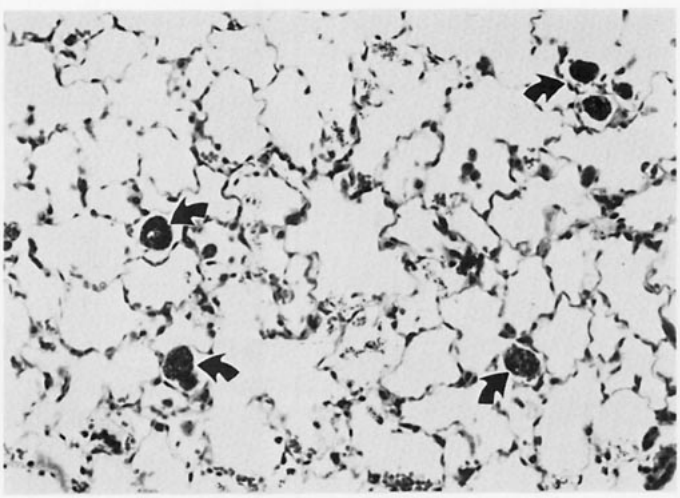

PLATE 7
Pigment-laden macrophages (arrows) and pigment within alveolar lumens in the lung of a male B6C3F$_1$ mouse exposed to 5 mg nickel oxide/m^3 by inhalation for 2 years. H&E; 175×

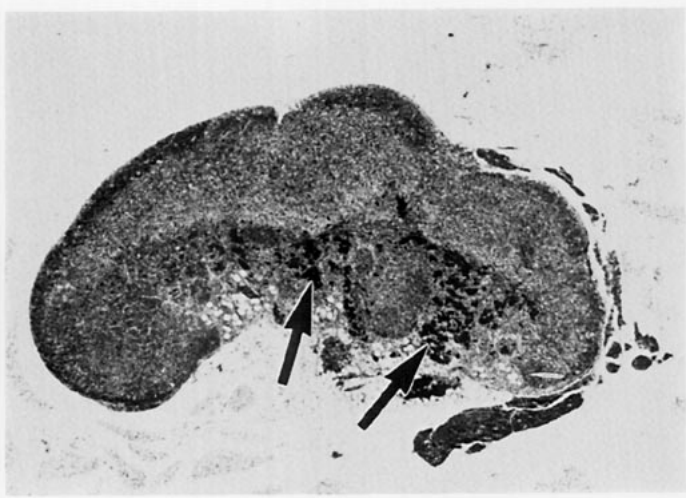

PLATE 8
Black pigment (arrows) in the bronchial lymph node of a male B6C3F$_1$ mouse exposed to 5 mg nickel oxide/m^3 by inhalation for 2 years. H&E; 25×

DISCUSSION AND CONCLUSIONS

Occupational exposure to nickel oxide may occur during refining and processing operations, in high temperature operations such as production of stainless steel, and in other industrial settings (Doll *et al.*, 1990). No previous 2-year studies have been reported that establish toxic dose-response relationships or toxic effects in organs other than the lung after inhalation exposure to nickel oxide in rats or mice.

In the 16-day (1.2 to 30 mg nickel oxide/m^3, equivalent to 0.9 to 23.6 mg nickel/m^3) and 13-week studies (0.6 to 10 mg nickel oxide/m^3, equivalent to 0.4 to 7.9 mg nickel/m^3), there were no chemical-related deaths in rats or mice. There were no biologically significant chemical-related effects on sperm morphology or vaginal cytology in rats or mice. The major toxic effects were in the lung, as evidenced by an exposure-related increase in lung weights and the occurrence of pigment and inflammation. In both the 16-day and 13-week studies, pigment and lymphoid hyperplasia occurred in the respiratory tract lymph nodes.

Analysis of bronchoalveolar lavage fluid has been used in human medicine for diagnosing the type or stage of various forms of interstitial lung disease and as a rapid *in vivo* method of evaluation of lung injury in toxicologic studies (Henderson *et al.*, 1985). In these 13-week studies of nickel oxide, evaluation of bronchoalveolar lavage fluid indicated the presence of an inflammatory response in the lung of rats exposed to 2.5 and 10 mg/m^3 and mice exposed to 10 mg/m^3 (Benson *et al.*, 1989). This increase was mostly due to an increase in the number of alveolar macrophages, although numbers of polymorphonuclear leukocytes were also significantly increased. Nickel oxide exposure resulted in decreased alveolar macrophage phagocytic activity and increased numbers of nucleated cells in lung lavage samples (Haley *et al.*, 1990). No nasal lesions were observed in either rats or mice in the 13-week studies, which contrasts with the findings for the more water-soluble nickel compounds (nickel sulfate hexahydrate and nickel subsulfide). Toxic effects were more severe in rats than in mice.

In this series of 16-day and 13-week nickel compound studies, nickel oxide was the least toxic, followed by nickel subsulfide and nickel sulfate hexahydrate, which was the most toxic (Tables 30 and 31). This is reflected by the increased mortality and reduced body weight gain or body weight loss seen with nickel sulfate hexahydrate and nickel subsulfide but not nickel oxide. The lung and nasal toxicity reflects the relative solubility of the nickel compounds in water and biological fluids, with the most soluble nickel compound (nickel sulfate hexahydrate) being the most toxic. The soluble nickel compounds are thought to be more toxic than the insoluble nickel compounds because nickel ions can diffuse across the cell membrane and interact with cytoplasmic proteins, thereby causing toxicity. Alternatively, the water-insoluble nickel compounds may be phagocytized and may not cause as extensive damage to cytoplasmic components of the alveolar/bronchiolar epithelium (Lee *et al.*, 1993; Costa *et al.*, 1994).

The spectrum of inflammatory lesions in the lungs of rats and mice after 13 weeks of exposure to nickel oxide was similar to that observed with other particles including nickel sulfate hexahydrate, nickel subsulfide, gallium arsenide (NTP unpublished data), gallium oxide (NTP unpublished data), and cadmium oxide (NTP, 1995). Lymphoid hyperplasia with or without inflammation was present in the respiratory tract lymph nodes of rats and mice from all of these studies. Nickel oxide pigment granules were present in the lung and respiratory lymph nodes; although pigment granules were not present in the lymph nodes of animals from the nickel sulfate hexahydrate, nickel subsulfide, or cadmium oxide studies, the morphologic appearance of the hyperplasia in the paracortical region of the lymph nodes was otherwise generally similar in each study.

In contrast to the findings with nickel sulfate hexahydrate and nickel subsulfide where the amount of nickel present in the lungs reached a steady state after a 13-week exposure period, the amount of nickel present in the lungs continued to increase during the 13-week exposure to nickel oxide; a

steady state was not reached. Even though the lungs of rats and mice exposed to nickel oxide contained more nickel than the lungs of animals exposed to nickel sulfate hexahydrate or nickel subsulfide (Table 32), the toxic effects were less severe at 13 weeks.

The threshold limit value for water-insoluble nickel compounds is 1 mg/m^3. In the 13-week studies of nickel oxide, a no-observed-adverse-effect level was not reached in either rats or mice; the histopathologic changes observed at the lowest exposure evaluated (0.6 mg nickel oxide/m^3) were subtle and were not necessarily indicative of severe lung toxicity.

The highest exposure concentrations for these 2-year studies were limited to 2.5 mg/m^3 for rats and 5 mg/m^3 for mice, because of the increased severity and spectrum of inflammatory lesions in the lung and increased lung weights that occurred at the higher exposure concentrations in the 13-week studies. The nickel compound exposure concentrations for the 16-day, 13-week, and 2-year nickel studies and their nickel equivalents are presented in Table 33.

Two-year exposure of rats and mice to nickel oxide by inhalation had no effect on survival. Mean body weights of 2.5 mg/m^3 male and female rats and 1.25 mg/m^3 female rats were 2% to 10% lower than those of controls during the last year of the study. Mean body weights of 5 mg/m^3 male and female mice were also lower than controls during the last year of the study.

At 7 months and at 15 months, the amount of nickel in lungs was similar in males and females. The lung nickel burden represents the difference between the amount of nickel deposited in the lung and the amount removed by the clearance mechanisms. Inhaled particles deposited on the mucosal surface of the trachea, bronchi, or bronchioles are transported up the airways and from the lung through the ciliary activity of the respiratory epithelium, while particles reaching the alveolar region are phagocytized by alveolar macrophages and, to a lesser extent, other phagocytic inflammatory cells. Some alveolar macrophages migrate to the ciliated epithelium of the airways while others cross the alveolar epithelium to enter the interstitium and, finally, the lymphatics. Phagocytic cells reaching the lymphatics are transported in the lymph to the bronchial and mediastinal lymph nodes. In the current studies, the pigment in the lymph nodes probably represented the clearance of some of nickel oxide from the lungs. Depending on the physiochemical properties of the inhaled particles, they may be partially or completely degraded within phagolysosomes of the macrophages and soluble components released from the cell. Nickel oxide is relatively insoluble in biologic fluids, and a relatively large amount of nickel oxide remains in the lung.

The carcinogenic response in the lung of rats exposed to nickel oxide was considered to be chemical related because the incidence of lung neoplasms in the 1.25 and 2.5 mg/m^3 groups exceeded the historical control rate at this laboratory, and the effect was observed in both males and females. The incidences of lung neoplasms in 1.25 mg/m^3 males (6/53, 11%) and females (6/53, 11%) and 2.5 mg/m^3 males (4/52, 8%) and females (5/54, 9%) were significantly greater ($P<0.05$) than the historical control incidences at Lovelace Inhalation Toxicology Research Institute, which are 1.4% (3/210) for males and 1.9% (4/208) for females. Some of these alveolar/bronchiolar neoplasms also had morphologic features (prominent scirrhous reaction and squamous differentiation) that were different from the spontaneous alveolar/bronchiolar neoplasms in control rats.

The incidence of alveolar/bronchiolar adenoma in the 2.5 mg/m^3 group of female mice was significantly greater than that of the controls and exceeded the historical control range from NTP inhalation studies. The incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in 1.25 mg/m^3 females was significantly greater than that of the controls, and the incidences in 1.25 and 2.5 mg/m^3 females exceeded the historical control range for inhalation studies. However, the incidences of these neoplasms were not increased at the highest exposure concentration (5 mg/m^3) in females.

The level of nickel in the lung was measured at various time points in the 2-year studies (Table 32), and these measurements represent the difference between the amount of nickel deposited and the amount cleared during a specified time frame. In the 2-year nickel oxide study, there was 300 to 1,100 μg nickel/g lung at 15 months; in the 2-year nickel subsulfide study, there was 3 to 7 μg nickel/g lung. Thus, the amount of nickel in the lung (as measured in these studies) does not predict or parallel the lung neoplasm response. The type of nickel compound is important in the eventual carcinogenic response, and under the conditions of these studies, the nickel

compound that was more rapidly cleared from the lungs (nickel subsulfide) produced a stronger carcinogenic response than the nickel compound retained in the lungs (nickel oxide).

The pulmonary and lung neoplasm responses observed in the nickel oxide and nickel subsulfide studies were chemically related; these responses occurred at exposure concentrations of 1.25 and 2.5 mg/m^3 nickel oxide and 0.15 and 1 mg/m^3 nickel subsulfide. There is no evidence for particle overload; nickel subsulfide levels at 15 months remained below 30 μg nickel/g lung, and while lung nickel levels increased in the nickel oxide studies to 1,000 μg/g lung, the levels approached steady state. In contrast, rat carcinogenicity studies with other relatively nontoxic particles (i.e., titanium dioxide, talc, or chromium dioxide) required higher aerosol concentrations (10 mg/m^3 or greater) to produce a lung neoplasm response. For example, the carcinogenic response in the rat lung reported in the NTP talc studies (NTP, 1993a) was observed at 18 mg/m^3; at this exposure concentration, approximately 25 mg talc/g lung was recorded at 18 months and 2 years. Similarly in the titantium dioxide inhalation studies in rats (Lee *et al.*, 1985), a lung neoplasm response was observed only at an exposure level of 250 mg/m^3, suggesting that the response may be related to accumulation of nontoxic particles.

Comparisons could be made of the types of lung neoplasms observed after inhalation of various chemicals at various levels of concentration. For example, relatively low levels of exposure to nickel (NTP, 1996a,b) or cadmium (NTP, 1995) produce neoplastic responses in rats. Intermediate exposure levels of diesel exhaust (3.5 to 7 mg/m^3; Mauderly *et al.*, 1987; Mauderly, 1994) and talc (18 mg/m^3; NTP, 1993a) produce carcinogenic effects in the lungs of rats. Higher exposure concentrations of antimony trioxide (45 mg/m^3; Groth *et al.*, 1986) and titanium dioxide (250 mg/m^3; Lee *et al.*, 1985) are required to produce similar effects in rats. Comparisons could also be made of the histopathologic nature of the lung neoplasms and of the molecular changes involved in the response.

A number of studies have reported sarcomas at the site of nickel oxide injection into the muscle or the pleural or peritoneal cavity of rodents (Table 3). In one inhalation study in hamsters exposed to a nickel oxide concentration of 50 mg/m^3, there were extensive nonneoplastic pulmonary lesions but no increase in lung neoplasms (Wehner *et al.*, 1975, 1979). Intratracheal administration of nickel oxide to female rats also caused a significant increase in adenocarcinoma and squamous cell carcinoma of the lung (Pott *et al.*, 1987).

Some generalities can be made about the comparative lung pathology in rats and mice after 2 years of exposure to nickel oxide, nickel subsulfide, or nickel sulfate hexahydrate. Pigment was observed in the lungs and bronchial lymph nodes of rats and mice exposed to nickel oxide but not in the lungs of animals in the nickel subsulfide or nickel sulfate hexahydrate studies. All three studies were similar in that mice were less susceptible to proliferative and fibrotic lung lesions than rats exposed to the same compound. Morphologic features of the proliferative lesions in rats exposed to nickel oxide or nickel subsulfide were clearly different from spontaneous lesions in control rats. Five of the alveolar/bronchiolar carcinomas in rats exposed to nickel oxide and four of the alveolar/bronchiolar carcinomas and two of the alveolar/bronchiolar adenomas in rats exposed to nickel subsulfide had marked squamous differentiation. Alveolar/bronchiolar neoplasms in exposed mice from all the studies and in rats exposed to nickel sulfate hexahydrate had morphologic features similar to those observed in spontaneously occurring tumors.

The nonneoplastic lung lesions in nickel oxide exposed rats had evidence of recurrent parenchymal damage secondary to inflammation. The resulting fibrosis and consolidation were multifocally extensive in many nickel oxide exposed rats, differing greatly from the minute fibrotic lesions that were occasionally observed in control rats. Similar exposure-related fibrotic lesions were also observed in nickel subsulfide exposed rats but not in nickel sulfate hexahydrate exposed rats. There were similar incidences, appearances, and severities of spontaneous lesions in the lungs of control rats and mice in the three nickel studies.

With the exception of pigment observed in the nickel oxide study, nonneoplastic lesions in the lungs of exposed mice were similar in all three nickel compound studies. The components of the inflammatory reaction (intra-alveolar protein and macrophages; mononuclear inflammatory cells around vessels; and multifocal intra-alveolar aggregates of inflammatory

cells) were similar in exposed mice in all three studies. Inflammatory foci with neutrophils and necrotic cell debris were relatively common in mice exposed to nickel sulfate hexahydrate, while inflammatory foci in mice exposed to nickel oxide and nickel subsulfide were predominantly mononuclear cells with little evidence of necrotic cell debris.

The inflammatory lesions in the lung were similar to those reported in rodents exposed to talc (NTP, 1993a), cadmium compounds (Aufderheide *et al.*, 1989), titanium dioxide (Lee *et al.*, 1985), chromium dioxide (Lee *et al.*, 1988), antimony trioxide and antimony ore concentrate (Groth *et al.*, 1986), or volcanic ash (Wehner *et al.*, 1986). Aerosols of each of these particulate substances were reported to elicit pulmonary inflammation (characterized primarily by the accumulation of alveolar macrophages), hyperplasia, and, in some cases, squamous metaplasia of the alveolar epithelium and fibrosis.

In the NTP studies, more chemical-related lung neoplasms were observed in nickel oxide and nickel subsulfide exposed rats than in mice. In cadmium carcinogenicity inhalation studies performed at the Fraunhofer Institute, cadmium induced alveolar/bronchiolar neoplasms in rats but not in mice (Aufderheide *et al.*, 1989; Heinrich *et al.*, 1989; Thiedemann *et al.*, 1989; Glaser *et al.*, 1990; Takenaka *et al.*, 1990). In the series of approximately 450 chemical studies by NTP, the rat is more susceptible to the formation of lung neoplasms after exposure to metals (e.g., nickel oxide, nickel subsulfide), while the mouse is more susceptible to the formation of lung neoplasms after exposure to epoxide-forming chemicals (e.g., coumarin, NTP, 1993b; benzene, NTP, 1986; glycidol, NTP, 1990a). The mouse is also more susceptible than the rat to formation of lung neoplasms after exposure to halogenated chemicals (2,2-bis(bromomethyl)-1,3-propanediol, NTP, 1996c; 1,2-dibromo-3-chloropropane, NTP, 1982a; 1,2-dibromomethane, NCI, 1978a, NTP 1982b; 2,3-dibromo-1-propanol, NTP, 1994; 1,2-dichloroethane, NCI, 1978b; and tris(2,3-dibromopropyl)phosphate, NCI, 1978c).

The morphologic types of lung neoplasms induced by various particulates in rodents vary. In the talc studies, a significant increase in alveolar/bronchiolar neoplasms was observed only in female rats (NTP, 1993a), and the type of neoplasm was similar to that observed in the present nickel oxide studies. Other chemicals producing alveolar/bronchiolar neoplasms in rats after inhalation exposure include antimony trioxide (Groth *et al.*, 1986) and cadmium (Aufderheide *et al.*, 1989). Alternatively, most of the pulmonary neoplasms induced by quartz (Dagle *et al.*, 1986), volcanic ash (Wehner *et al.*, 1986), or chromium dioxide (Lee *et al.*, 1988) were squamous cell (epidermoid) carcinomas. In refinery workers, pulmonary neoplasms attributed to nickel exposure have been classified primarily as squamous cell carcinomas with fewer anaplastic carcinomas and adenocarcinomas (Sunderman *et al.*, 1989).

Lung tissue specimens from 39 nickel refinery workers showed increased lung nickel levels (Andersen and Svenes, 1989). The average nickel concentration for workers in roasting and smelting operations was 330 ± 380 μg nickel/g dry lung weight; for workers in electrolysis departments, 34 ± 48 μg/g; and for lung tissue from unexposed people, 0.76 ± 0.39 μg/g. Dry lung represents approximately 20% "wet" lung weight (Henderson and Escobedo, 1976). Workers who were diagnosed with lung cancer (14 cases) had the same lung nickel concentrations at autopsy as nickel workers (25 cases) who died of other causes. The lung nickel concentration was independent of smoking habits. Anderson and Svenes (1989) felt that the retained nickel in the lung was probably nickel oxide because an earlier study using energy dispersive X-ray analysis did not detect sulfides (e.g., Ni_3S_2) in the lung. This study also found that lung cancer occurred in workers from the electrolysis department (8/24) as well as those from the roasting and smelting operations (6/15) even though those from the electrolysis department had lower lung nickel levels.

Nasopharyngeal carcinoma in humans has been attributed to nickel exposure. The preponderance of these sinonasal neoplasms in humans have been classified as anaplastic, undifferentiated, or squamous cell carcinoma (Sunderman *et al.*, 1989). In the present rodent studies, the olfactory epithelium, rather than the respiratory or squamous mucosa, was the target site for chemical-related toxicity. Although the atrophic changes were present in the olfactory epithelium of rats and mice in the 13-week and 2-year studies of nickel subsulfide and nickel sulfate hexahydrate, the nasal mucosa was not affected in the nickel oxide study. Furthermore, after 2 years, there was no evidence of a chemical-related increase in the incidences of proliferative lesions in the nasal cavity

of rats or mice exposed to any of the three nickel compounds tested.

The increase in proliferative lesions of the adrenal medulla in male and female rats was considered to be chemical related. In male rats, the overall increase in benign and malignant pheochromocytomas was related primarily to an increase in malignant pheochromocytomas. In female rats, only the incidence of benign pheochromocytoma was increased, but the number of rats with bilateral pheochromocytoma and the number with hyperplasia were also increased in the 5 mg/m^3 group. A chemical-related increase in pheochromocytomas was also observed in male and female rats exposed to nickel subsulfide and in male and female rats exposed to talc (NTP, 1993a). However, similar increases were not observed in rats exposed to nickel sulfate hexahydrate or to other particulates including antimony trioxide or trisulfide (Groth *et al.*, 1986) and titanium dioxide (Lee *et al.*, 1988). Chemical-related increases in the incidences of pheochromocytoma have also been reported in rats exposed by inhalation to bromoethane (NTP, 1990b) and orally to 2-mercaptobenzothiazole (NTP, 1988) and reserpine (NCI, 1982). The mechanism for this increased incidence of adrenal medulla neoplasms is not known. There was no morphologic evidence that the pigment granules of phagocytized nickel oxide reached the adrenal gland, suggesting that the mechanism for the carcinogenic response in the adrenal gland may be related to factors other than direct interaction of the chemical with adrenal cells.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *some evidence of carcinogenic activity** of nickel oxide in male F344/N rats based on increased incidences of alveolar/bronchiolar adenoma or carcinoma (combined) and increased incidences of benign or malignant pheochromocytoma (combined) of the adrenal medulla. There was *some evidence of carcinogenic activity* of nickel oxide in female F344/N rats based on increased incidences of alveolar/bronchiolar adenoma or carcinoma (combined) and increased incidences of benign pheochromocytoma of the adrenal medulla. There was *no evidence of carcinogenic activity* of nickel oxide in male B6C3F$_1$ mice exposed to 1.25, 2.5, or 5 mg/m^3. There was *equivocal evidence of carcinogenic activity* of nickel oxide in female B6C3F$_1$ mice based on the marginally increased incidences of alveolar/bronchiolar adenoma in 2.5 mg/m^3 females and of alveolar/bronchiolar adenoma or carcinoma (combined) in 1.25 mg/m^3 females.

Exposure of rats to nickel oxide by inhalation for 2 years resulted in inflammation and pigmentation in the lung, lymphoid hyperplasia and pigmentation in the bronchial lymph nodes, and hyperplasia of the adrenal medulla (females). Exposure of mice to nickel oxide by inhalation for 2 years resulted in bronchialization, proteinosis, inflammation, and pigmentation in the lung and lymphoid hyperplasia and pigmentation in the bronchial lymph nodes.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

TABLE 30
Selected Results in the 16-Day Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide[a]

Dose mg/m³ (mg Ni/m³)	Nickel Sulfate Hexahydrate						Nickel Subsulfide						Nickel Oxide					
	0	3.5 (0.7)	7 (1.4)	15 (3.1)	30 (6.1)	60 (12.2)	0	0.6 (0.44)	1.2 (0.88)	2.5 (1.83)	5 (3.65)	10 (7.33)	0	1.2 (0.9)	2.5 (2.0)	5 (3.9)	10 (7.9)	30 (23.6)
Male Rats																		
Survival	5	5	5	5	5	3	5	5	5	5	5	4	5	5	5	5	5	5
Final Mean Body Weights (Relative to Controls)	—	72%	60%	56%	55%	45%	—	109%	105%	92%	72%	52%	—	99%	101%	99%	99%	96%
Absolute Lung Weights[b]	0.98	1.44**	1.45**	1.40*	1.40*	1.62**	1.13	1.41	1.60*	1.59*	1.82**	1.54**	1.06	1.00	1.06	0.96	1.20*	1.36**
Female Rats																		
Survival	5	5	5	5	4	0	5	5	5	5	5	5	5	5	5	5	5	5
Final Mean Body Weights (Relative to Controls)	—	82%	71%	68%	63%	—	—	99%	97%	91%	78%	57%	—	103%	103%	104%	101%	99%
Absolute Lung Weights	0.76	1.28*	1.28*	1.32*	1.40**	1.52**	0.82	1.12**	1.12**	1.36**	1.42**	1.25**	0.78	0.86	0.90	0.82	1.04**	1.12**
Male Mice																		
Survival	5	5	0	0	0	0	4	5	4	5	5	0	5	5	5	4	5	5
Final Mean Body Weights (Relative to Controls)	—	95%	—	—	—	—	—	99%	90%	92%	86%	—	—	100%	100%	98%	102%	94%
Absolute Lung Weights	0.20	0.24	0.40**	0.36**	0.36**	0.38**	0.22	0.20	0.22	0.28	0.31**	0.38**	0.20	0.16	0.20	0.13**	0.20	0.20
Female Mice																		
Survival	5	5	0	0	0	0	4	5	5	5	5	0	5	5	5	5	5	5
Final Mean Body Weights (Relative to Controls)	—	96%	—	—	—	—	—	106%	104%	101%	99%	—	—	100%	96%	100%	95%	95%
Absolute Lung Weights	0.16	0.22	0.36**	0.36**	0.38**	0.40**	0.20	0.21	0.22	0.27	0.36*	0.25	0.16	0.16	0.14	0.18	0.12	0.20

* Significantly different ($P \leq 0.05$) from the control by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Survival data indicate number of animals surviving. Five animals initially in group. Final mean body weights are not presented for groups with 100% mortality.
[b] Organ weights are given in grams.

TABLE 31
Selected Results in the 13-Week Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide[a]

	Nickel Sulfate Hexahydrate						Nickel Subsulfide						Nickel Oxide					
Dose mg/m³ (mg Ni/m³)	0	0.12 (0.03)	0.25 (0.06)	0.5 (0.11)	1 (0.22)	2 (0.44)	0	0.15 (0.11)	0.3 (0.22)	0.6 (0.44)	1.2 (0.88)	2.5 (1.83)	0	0.6 (0.4)	1.2 (0.9)	2.5 (2.0)	5 (3.9)	10 (7.9)
Male Rats																		
Survival	10	10	10	10	10	9	10	10	10	10	10	10	10	10	10	9	10	10
Final Mean Body Weights (Relative to Controls)	—	99%	103%	96%	102%	95%	—	100%	95%	96%	99%	93%	—	103%	104%	99%	102%	100%
Absolute Lung Weights	1.35	1.25	1.51*	1.64**	2.14**	2.22**	1.33	1.74**	1.83**	2.30**	2.63**	2.42**	1.18	1.35**	1.47**	1.70**	1.91**	2.47**
Nonneoplastic Lung Lesions																		
Alveolar Macrophage, Hyperplasia	0	10	10	10	10	9	0	10	10	10	10	10	0	10	10	9	10	10
(Severity)[b]		(1.0)	(1.0)	(1.0)	(2.4)	(3.6)		(1.1)	(1.5)	(1.6)	(3.4)	(3.8)		(1.0)	(1.0)	(1.0)	(1.5)	(2.5)
Inflammation, Chronic Active	0	0	0	2	10	8	0	2	9	10	10	10	0	0	0	2	10	10
(Severity)				(1.0)	(1.5)	(1.3)		(1.0)	(1.3)	(1.8)	(2.9)	(3.7)				(1.0)	(1.7)	(3.0)
Inflammation, Granulomatous	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	2
(Severity)																	(2.0)	(3.0)
Interstitial Infiltrate	1	0	1	5	10	9	0	0	1	10	9	8	0	0	1	2	10	10
(Severity)	(1.0)		(1.0)	(1.0)	(1.0)	(1.1)			(1.0)	(1.9)	(2.1)	(1.2)			(1.0)	(1.0)	(1.4)	(2.1)
Pigment	0	0	0	0	0	0	0	0	0	0	0	0	0	6	7	9	9	10
(Severity)														(1.0)	(1.0)	(1.0)	(1.0)	(1.8)
Nonneoplastic Nasal Lesions																		
Atrophy, Olfactory Epithelium	0	0	0	1	10	9	0	0	1	5	10	10	0	0	0	0	0	0

(continued)

TABLE 31
Selected Results in the 13-Week Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide (continued)

Dose mg/m³ (mg Ni/m³)	Nickel Sulfate Hexahydrate						Nickel Subsulfide						Nickel Oxide					
	0	0.12 (0.03)	0.25 (0.06)	0.5 (0.11)	1 (0.22)	2 (0.44)	0	0.15 (0.11)	0.3 (0.22)	0.6 (0.44)	1.2 (0.88)	2.5 (1.83)	0	0.6 (0.4)	1.2 (0.9)	2.5 (2.0)	5 (3.9)	10 (7.9)
Female Rats																		
Survival	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Final Mean Body Weights (Relative to Controls)	—	96%	98%	98%	101%	95%	—	101%	104%	101%	100%	99%	—	101%	101%	98%	98%	100%
Absolute Lung Weights	1.02	1.02	1.16**	1.34**	1.72**	1.72**	1.01	1.29**	1.39**	1.82**	1.85**	1.81**	0.98	1.03	1.13*	1.55**	1.61**	2.11**
Nonneoplastic Lung Lesions																		
Alveolar Macrophage, Hyperplasia	0	8	10	10	10	10	0	10	10	10	10	10	0	10	8	10	10	10
(Severity)		(1.0)	(1.0)	(1.1)	(2.2)	(3.6)		(1.0)	(1.7)	(1.8)	(2.9)	(3.8)		(1.0)	(1.0)	(1.0)	(1.4)	(2.2)
Inflammation, Chronic Active	0	0	0	4	10	10	0	3	9	10	10	10	0	0	0	1	7	7
(Severity)				(1.0)	(1.3)	(1.0)		(1.0)	(1.0)	(1.9)	(2.6)	(3.8)				(1.0)	(1.3)	(2.7)
Inflammation, Granulomatous	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	4
(Severity)																	(2.1)	(2.0)
Interstitial Infiltrate	0	0	0	6	10	10	0	0	2	9	10	5	0	0	0	2	10	10
(Severity)				(1.0)	(1.0)	(1.0)			(1.0)	(1.7)	(2.4)	(1.6)				(1.0)	(1.2)	(1.8)
Pigment	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	8	8	10
(Severity)															(1.0)	(1.0)	(1.0)	(1.2)
Nonneoplastic Nasal Lesions																		
Atrophy, Olfactory Epithelium	0	0	1	2	10	10	0	0	0	8	9	10	0	0	0	0	0	0

(continued)

TABLE 31
Selected Results in the 13-Week Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide (continued)

	Nickel Sulfate Hexahydrate						Nickel Subsulfide						Nickel Oxide					
Dose mg/m³ (mg Ni/m³)	**0**	**0.12 (0.03)**	**0.25 (0.06)**	**0.5 (0.11)**	**1 (0.22)**	**2 (0.44)**	**0**	**0.15 (0.11)**	**0.3 (0.22)**	**0.6 (0.44)**	**1.2 (0.88)**	**2.5 (1.83)**	**0**	**0.6 (0.4)**	**1.2 (0.9)**	**2.5 (2.0)**	**5 (3.9)**	**10 (7.9)**
Male Mice																		
Survival	6	8[c]	10	10	10	10	8	10	10	8	9	10	10	10	10	10	10	9
Final Mean Body Weights (Relative to Controls)	—	105%	100%	104%	104%	102%	—	102%	106%	103%	101%	97%	—	101%	99%	97%	98%	97%
Absolute Lung Weights	0.20	0.20	0.20	0.21	0.25**	0.31**	0.19	0.20	0.22	0.21	0.23*	0.28**	0.21	0.22	0.21	0.21	0.24	0.29**
Nonneoplastic Lung Lesions																		
Alveolar Macrophage, Hyperplasia	0	0	0	10	10	10	0	0	8	8	9	10	0	10	10	10	10	9
(Severity)				(1.0)	(1.0)	(1.0)			(1.0)	(1.0)	(2.0)	(2.2)		(1.0)	(1.0)	(1.0)	(1.0)	(1.1)
Fibrosis, Focal	0	0	0	0	2	10	0	0	0	0	5	10	0	0	0	0	0	0
(Severity)					(1.5)	(2.0)					(1.6)	(2.1)						
Inflammation, Chronic Active	0	0	0	0	2	2	0	0	0	0	5	7	0	0	0	0	0	3
(Severity)					(1.0)	(1.5)					(1.2)	(1.6)						(1.0)
Inflammation, Granulomatous	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3
(Severity)																		(1.0)
Interstitial Infiltrate	0	0	0	0	2	8	0	1	0	2	3	2	0	0	0	1	3	8
(Severity)					(1.0)	(1.0)		(1.0)		(1.0)	(1.2)	(1.5)				(1.0)	(1.0)	(1.0)
Pigment	0	0	0	0	0	0	0	0	0	0	0	0	0	10	10	10	10	9
(Severity)														(1.0)	(1.0)	(1.0)	(1.0)	(1.0)
Nonneoplastic Nasal Lesions																		
Atrophy, Olfactory Epithelium	0	0	0	0	0	10	0	0	0	5	5	10	0	0	0	0	0	0

(continued)

TABLE 31
Selected Results in the 13-Week Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide (continued)

	Nickel Sulfate Hexahydrate						Nickel Subsulfide						Nickel Oxide					
Dose mg/m³	**0**	**0.12**	**0.25**	**0.5**	**1**	**2**	**0**	**0.15**	**0.3**	**0.6**	**1.2**	**2.5**	**0**	**0.6**	**1.2**	**2.5**	**5**	**10**
(mg Ni/m³)		**(0.03)**	**(0.06)**	**(0.11)**	**(0.22)**	**(0.44)**		**(0.11)**	**(0.22)**	**(0.44)**	**(0.88)**	**(1.83)**		**(0.4)**	**(0.9)**	**(2.0)**	**(3.9)**	**(7.9)**
Female Mice																		
Survival	7	10	10	10	10	10	10	8	10	9	10	8	9	10	7	10	10	9
Final Mean Body Weights (Relative to Controls)	—	105%	104%	105%	103%	97%	—	101%	100%	101%	101%	99%	—	97%	100%	96%	94%	97%
Absolute Lung Weights	0.20	0.20	0.20	0.20	0.22	0.27**	0.19	0.18	0.20	0.21	0.26**	0.29**	0.20	0.20	0.19	0.21	0.22	0.27**
Nonneoplastic Lung Lesions																		
Alveolar Macrophage, Hyperplasia	0	0	0	10	10	10	0	0	4	9	10	10	0	10	7	10	10	9
(Severity)				(1.0)	(1.0)	(1.0)			(1.0)	(1.0)	(2.4)	(2.6)		(1.0)	(1.0)	(1.0)	(1.1)	(1.0)
Fibrosis, Focal	0	0	0	0	1	8	0	0	0	0	1	9	0	0	0	0	0	0
(Severity)					(1.0)	(1.5)					(2.0)	(1.6)						
Inflammation, Chronic Active	0	0	0	0	1	9	0	0	0	0	10	7	0	0	0	0	1	3
(Severity)					(1.0)	(1.9)					(1.5)	(2.0)					(1.0)	(1.1)
Inflammation, Granulomatous	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
(Severity)																		(1.0)
Interstitial Infiltrate	1	0	0	1	1	8	0	2	3	4	9	8	0	1	0	4	6	8
(Severity)	(1.0)			(1.0)	(1.0)	(1.3)		(1.0)	(1.0)	(1.0)	(1.4)	(1.7)		(1.0)		(1.0)	(1.1)	(1.1)
Pigment	0	0	0	0	0	0	0	0	0	0	0	0	0	10	7	10	10	9
(Severity)														(1.0)	(1.0)	(1.0)	(1.0)	(1.0)
Nonneoplastic Nasal Lesions																		
Atrophy, Olfactory Epithelium	0	0	0	0	0	5	0	0	0	1	6	10	0	0	0	0	0	0

* Significantly different ($P \leq 0.05$) from the control by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Survival data indicate number of animals surviving. Ten animals initially in group. Final mean body weights are not presented for groups with 100% mortality.
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Nine animals initially in group.

TABLE 32
Lung Burden Analyses in the 16-Day, 13-Week, and 2-Year Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide[a]

Dose mg/m³ (mg Ni/m³)	Nickel Sulfate Hexahydrate (22.3% Ni)							Nickel Subsulfide (73.3% Ni)					Nickel Oxide (78.6% Ni)					
	0	0.12 (0.03)	0.5 (0.06)	2 (0.44)	3.5 (0.7)	15 (3.1)	30 (6.1)	0	0.15 (0.11)	0.6 (0.44)	2.5 (1.83)	10 (7.33)	0	0.6 (0.4)	1.2 (0.9)	2.5 (2.0)	5 (3.9)	10 (7.9)
16-Day Studies																		
Male Rats	–[b]				5	9	8	–		7	18	67	–		42		108	267
Female Rats	–				8	11	9	–		9	19	77	–		54		122	340
Male Mice	–				3			–		10	20	13	–		32	46	84	
Female Mice	–				4			–		8	20	8	–		31	43	71	
13-Week Studies																		
Male Rats	–	–	1	6				–	5	7	18		–	80		181		524
Female Rats	–	–	2	7				–	5	7	17							
Male Mice	–	–	–	1				–	3	11	17		–	42		202		736
Female Mice	–	–	–	4				–	6	13	23							

(continued)

TABLE 32
Lung Burden Analyses in the 16-Day, 13-Week, and 2-Year Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide (continued)

Dose mg/m³ (mg Ni/m³)	Nickel Sulfate Hexahydrate (22.3% Ni)						Nickel Subsulfide (73.3% Ni)					Nickel Oxide (78.6% Ni)					
	0	0.12 (0.03)	0.25 (0.06)	0.5 (0.11)	1 (0.22)	2 (0.44)	0	0.15 (0.11)	0.6 (0.44)	1 (0.73)	1.2 (0.88)	0	0.62 (0.5)	1.25 (1.0)	2.5 (2.0)	5 (3.9)	10 (7.9)
7-Month Interim Evaluation																	
Male Rats	–	–	–	1			–	6		9		–	175	388	701		
Female Rats	–	–	–	1			–	6		9		–	173	477	713		
Male Mice	–		1	1	2		–		10		11	–		162	442	1,034	
Female Mice	–		1	2	2		–		10		14	–		169	533	861	
15-Month Interim Evaluation																	
Male Rats	–	–	–	1			–	4		3		–	328	746	1,116		
Female Rats	–	–	–	2			–	4		7		–	262	706	949		
Male Mice	–		1	1	2		–		15		26	–		331	959	1,798	
Female Mice	–		1	2	2		–		12		20	–		451	1,237	2,258	

[a] Values represent mean amounts of nickel (μg Ni/g lung). Lung burden groups included five to seven animals.
[b] Results were below the limit of detection or quantitation.

TABLE 33
Comparison of Exposure Concentrations in the 16-Day, 13-Week, and 2-Year Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide[a]

	Amount of Compound	Amount of Nickel
16-Day Studies		
Nickel Sulfate Hexahydrate (22.3% Ni)	0, 3.5, 7, 15, 30, 60	0, 0.7, 1.4, 3.1, 6.1, 12.2
Nickel Subsulfide (73.3% Ni)	0, 0.6, 1.2, 2.5, 5, 10	0, 0.44, 0.88, 1.83, 3.65, 7.33
Nickel Oxide (78.6% Ni)	0, 1.2, 2.5, 5, 10, 30	0, 0.9, 2.0, 3.9, 7.9, 23.6
13-Week Studies		
Nickel Sulfate Hexahydrate (22.3% Ni)	0, 0.12, 0.25, 0.5, 1, 2	0, 0.03, 0.06, 0.11, 0.22, 0.44
Nickel Subsulfide (73.3% Ni)	0, 0.15, 0.3, 0.6, 1.2, 2.5	0, 0.11, 0.22, 0.44, 0.88, 1.83
Nickel Oxide (78.6% Ni)	0, 0.6, 1.2, 2.5, 5, 10	0, 0.4, 0.9, 2.0, 3.9, 7.9
2-Year Studies		
Nickel Sulfate Hexahydrate (22.3% Ni)		
Rats	0, 0.12, 0.25, 0.5	0, 0.03, 0.06, 0.11
Mice	0, 0.25, 0.5, 1	0, 0.06, 0.11, 0.22
Nickel Subsulfide (73.3% Ni)		
Rats	0, 0.15, 1	0, 0.11, 0.73
Mice	0, 0.6, 1.2	0, 0.44, 0.88
Nickel Oxide (78.6% Ni)		
Rats	0, 0.62, 1.25, 2.5	0, 0.5, 1.0, 2.0
Mice	0, 1.25, 2.5, 5	0, 1.0, 2.0, 3.9

[a] Amounts of nickel and nickel compounds are expressed in mg/m^3. Occupational exposure limits in the United States: 1 mg Ni/m^3 for nickel metals, 0.1 mg Ni/m^3 for soluble nickel compounds.

TABLE 34
Selected Results in the 2-Year Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide[a]

	Nickel Sulfate Hexahydrate (22.3% Ni)				Nickel Subsulfide (73.3% Ni)			Nickel Oxide (78.6% Ni)			
Dose mg/m³	0	0.12	0.25	0.5	0	0.15	1	0	0.62	1.25	2.5
(mg Ni/m³)		(0.03)	(0.06)	(0.11)		(0.11)	(0.73)		(0.5)	(1.0)	(2.0)
Male Rats											
Survival	16/54	16/55	18/55	21/55	13/53	21/53	18/53	14/54	15/53	15/53	12/52
Final Mean Body Weights											
(Relative to Controls)	—	99%	101%	98%	—	98%	85%	—	100%	95%	93%
Absolute Lung Weights											
7-Month Interim Evaluation	1.67	1.62	1.65	1.89	1.87	2.38**	3.48**	1.72	1.85	2.43**	2.59**
15-Month Interim Evaluation	2.12	2.48	2.50	3.00**	2.27	3.31**	6.84**	2.20	2.15	3.30**	4.09**
Alveolar/bronchiolar Proliferative Lesions and Neoplasms											
Alveolar Epithelial											
Hyperplasia, Focal or Atypical	3	2	3	2	2	6	11**	0	2	5*	3
Adenoma	0	0	0	2	0	3	6*	0	1	3	2
Carcinoma	2[b]	0	1	1	0	3	7*	1[b]	0	3	2
Adenoma or Carcinoma (Combined)	2[b]	0	1	3	0	6*	11**	1[b]	1	6[c]	4[c]
Adrenal Medulla Proliferative Lesions and Neoplasms											
Hyperplasia	28	20	18	26	26	22	10	25	27	26	24
Benign Pheochromocytoma	16	16	12	11	13	30**	38**	27	24	26	32
Malignant Pheochromocytoma	0	3	2	1	0	2	10**	0	0	1	6*
Benign or Malignant Pheochromocytoma	16	19	13	12	14	30**	42**	27	24	27	35**
Carcinogenic Activity		No evidence				Clear evidence			Some evidence		

(continued)

TABLE 34
Selected Results in the 2-Year Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide (continued)

	Nickel Sulfate Hexahydrate (22.3% Ni)				Nickel Subsulfide (73.3% Ni)			Nickel Oxide (78.6% Ni)			
Dose mg/m³ (mg Ni/m³)	0	0.12 (0.03)	0.25 (0.06)	0.5 (0.11)	0	0.15 (0.11)	1 (0.73)	0	0.62 (0.5)	1.25 (1.0)	2.5 (2.0)
Female Rats											
Survival	22/52	17/53	28/53	29/54	26/53	25/53	28/52	21/53	26/53	20/53	26/54
Final Mean Body Weights (Relative to Controls)	—	97%	97%	94%	—	96%	78%	—	96%	92%	90%
Absolute Lung Weights											
7-Month Interim Evaluation	1.25	1.22	1.22	1.45*	1.31	1.75**	2.59**	1.14	1.31*	1.65**	1.78**
15-Month Interim Evaluation	1.37	1.57	1.49	1.82**	1.52	2.52**	4.14**	1.56	1.79	2.41**	3.02**
Alveolar/bronchiolar Proliferative Lesions and Neoplasms											
Alveolar Epithelial Hyperplasia, Focal or Atypical	5	3	7	9	2	10*	11**	2	1	6	6
Adenoma	0	0	0	1	2	5	5	1	0	1	4
Carcinoma	0	0	0	0	0	1[b]	4	0	0	5*	1
Adenoma or Carcinoma (Combined)	0	0	0	1	2	6[b,d]	9*	1	0	6[d]	5[d]
Adrenal Medulla Proliferative Lesions and Neoplasms											
Hyperplasia	6	4	8	8	5	11	16**	8	12	14	22**
Benign Pheochromocytoma	2	4	2	3	2	7	36**	4	7	6	18**
Malignant Pheochromocytoma	0	0	0	0	1	0	1	0	0	0	0
Benign or Malignant Pheochromocytoma	2	4	2	3	3	7	36**	4	7	6	18**
Carcinogenic Activity		No evidence				Clear evidence			Some evidence		

(continued)

TABLE 34
Selected Results in the 2-Year Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide (continued)

	Nickel Sulfate Hexahydrate (22.3% Ni)				Nickel Subsulfide (73.3% Ni)			Nickel Oxide (78.6% Ni)			
Dose mg/m³	**0**	**0.25**	**0.5**	**1**	**0**	**0.6**	**1.2**	**0**	**1.25**	**2.5**	**5**
(mg Ni/m³)		**(0.06)**	**(0.11)**	**(0.22)**		**(0.44)**	**(0.88)**		**(1.0)**	**(2.0)**	**(3.9)**
Male Mice											
Survival	26/61	23/61	24/62	25/61	26/61	25/59	26/58	19/57	23/67	29/66	23/69
Final Mean Body Weights											
(Relative to Controls)	—	94%	97%	91%	—	92%	92%	—	93%	93%	93%
Absolute Lung Weights											
7-Month Interim Evaluation	0.21	0.20	0.22	0.23	0.24	0.27	0.34**	0.19	0.21	0.24**	0.24**
15-Month Interim Evaluation	0.24	0.25	0.26	0.31**	0.23	0.40**	0.41**	0.23	0.25	0.31*	0.38**
Alveolar/bronchiolar Proliferative Lesions and Neoplasms											
Alveolar Epithelial											
Hyperplasia, Focal	0	0	0	0	0	0	0	1	1	2	0
Adenoma	5	5	3	5	6	3	2	7	5	6	11
Carcinoma	9	13	4	3	7	2	4	4	10	9	6
Adenoma or Carcinoma (Combined)	13	18	7	8	13	5	6	9	14	15	14
Carcinogenic Activity		No evidence				No evidence			No evidence		

(continued)

TABLE 34
Selected Results in the 2-Year Inhalation Studies of Nickel Sulfate Hexahydrate, Nickel Subsulfide, and Nickel Oxide (continued)

Dose mg/m³ (mg Ni/m³)	Nickel Sulfate Hexahydrate (22.3% Ni) 0	0.25 (0.06)	0.5 (0.11)	1 (0.22)	Nickel Subsulfide (73.3% Ni) 0	0.6 (0.44)	1.2 (0.88)	Nickel Oxide (78.6% Ni) 0	1.25 (1.0)	2.5 (2.0)	5 (3.9)
Female Mice											
Survival	34/61	39/60	45/60	37/60	38/58	34/59	38/60	41/64	40/66	42/63	38/64
Final Mean Body Weights (Relative to Controls)	—	91%	94%	88%	—	90%	86%	—	96%	94%	90%
Absolute Lung Weights											
7-Month Interim Evaluation	0.22	0.21	0.22	0.25	0.19	0.26*	0.29**	0.18	0.21	0.23	0.23
15-Month Interim Evaluation	0.24	0.24	0.28	0.33**	0.26	0.39**	0.50**	0.25	0.26	0.29	0.34**
Alveolar/bronchiolar Proliferative Lesions and Neoplasms											
Alveolar Epithelial Hyperplasia, Focal	0	1	1	0	0	0	0	0	0	1	0
Adenoma	3	3	2	0	3	1	1	2	4	10*	3
Carcinoma	4	3	9	2	7	1	2	4	11	4	5
Adenoma or Carcinoma (Combined)	7	6	10	2	9	2	3	6	15*	12	8
Carcinogenic Activity		No evidence				No evidence			Equivocal evidence		

* Significantly different ($P \leq 0.05$) from the control by Williams' or Dunnett's test (lung weights) or the logistic regression test (incidences).
** $P \leq 0.01$
[a] Survival data indicate number of animals surviving/number initially in group.
[b] Includes data for squamous cell carcinoma
[c] Significantly different ($P < 0.05$) from the Lovelace Inhalation Toxicology Research Institute historical controls [3/210 (1.4%)]
[d] Significantly different ($P < 0.05$) from the Lovelace Inhalation Toxicology Research Institute historical controls [4/208 (1.9%)]

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF NICKEL OXIDE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Disposition Summary				
Animals initially in study	65	65	65	65
7-Month interim evaluation	6	7	7	7
15-Month interim evaluation	5	5	5	5
Early deaths				
Moribund	39	35	32	36
Natural deaths	1	3	6	4
Survivors				
Died last week of study			1	1
Terminal sacrifice	14	15	14	11
Missexed				1
Animals examined microscopically	65	65	65	64
Systems Examined At 7 Months With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
15-Month Interim Evaluation				
Endocrine System				
Adrenal medulla	(5)	(5)	(5)	(5)
Pheochromocytoma benign			2 (40%)	
Pituitary gland	(5)	(5)	(5)	(5)
Pars distalis, adenoma		1 (20%)		
Thyroid gland	(5)	(5)	(5)	(5)
C-cell, adenoma	1 (20%)		1 (20%)	
Genital System				
Testes	(5)	(5)	(5)	(5)
Bilateral, interstitial cell, adenoma				1 (20%)
Interstitial cell, adenoma	3 (60%)	4 (80%)		3 (60%)
Integumentary System				
Skin				(1)
Sebaceous gland, adenoma				1 (100%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine large, colon	(54)	(53)	(53)	(52)
Intestine large, rectum	(54)	(53)	(52)	(52)
Anus, leiomyoma			1 (2%)	
Intestine large, cecum	(54)	(53)	(52)	(51)
Intestine small, duodenum	(54)	(52)	(53)	(52)
Intestine small, jejunum	(54)	(53)	(53)	(52)
Intestine small, ileum	(54)	(53)	(53)	(51)
Fibroma		1 (2%)		
Liver	(54)	(53)	(53)	(52)
Fibrous histiocytoma, metastatic				1 (2%)
Hemangioma		1 (2%)		
Hepatocellular carcinoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Hepatocellular carcinoma, multiple			1 (2%)	
Hepatocellular adenoma	3 (6%)	5 (9%)	3 (6%)	2 (4%)
Hepatocellular adenoma, multiple		1 (2%)		
Histiocytic sarcoma, metastatic, skin				1 (2%)
Mesentery	(1)	(1)		(1)
Pancreas	(54)	(53)	(53)	(52)
Salivary glands	(54)	(53)	(53)	(52)
Squamous cell carcinoma			1 (2%)	
Stomach, forestomach	(54)	(53)	(53)	(52)
Stomach, glandular	(54)	(53)	(53)	(52)
Tongue			(1)	
Squamous cell carcinoma			1 (100%)	
Cardiovascular System				
Heart	(54)	(53)	(53)	(52)
Carcinoma, metastatic, lung				1 (2%)
Endocrine System				
Adrenal cortex	(54)	(53)	(53)	(52)
Adenoma		1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Endocrine System (continued)				
Adrenal medulla	(54)	(52)	(53)	(52)
Pheochromocytoma malignant			1 (2%)	6 (12%)
Pheochromocytoma benign	17 (31%)	13 (25%)	17 (32%)	16 (31%)
Bilateral, pheochromocytoma benign	10 (19%)	11 (21%)	9 (17%)	16 (31%)
Islets, pancreatic	(54)	(53)	(53)	(52)
Adenoma	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Adenoma, multiple		1 (2%)		
Carcinoma	1 (2%)	1 (2%)	2 (4%)	
Parathyroid gland	(50)	(50)	(49)	(49)
Adenoma	1 (2%)	1 (2%)	1 (2%)	
Pituitary gland	(53)	(52)	(52)	(52)
Pars distalis, adenoma	24 (45%)	18 (35%)	16 (31%)	12 (23%)
Pars intermedia, carcinoma			1 (2%)	
Thyroid gland	(54)	(53)	(52)	(52)
C-cell, adenoma	6 (11%)	5 (9%)	4 (8%)	2 (4%)
C-cell, carcinoma	1 (2%)		1 (2%)	
Follicular cell, adenoma	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Follicular cell, carcinoma	1 (2%)			1 (2%)
General Body System				
Tissue NOS	(3)	(2)	(2)	(4)
Basal cell carcinoma				1 (25%)
Carcinoma, metastatic, lung				1 (25%)
Fibrosarcoma				1 (25%)
Lipoma			2 (100%)	
Oral, osteosarcoma	1 (33%)			
Genital System				
Epididymis	(54)	(53)	(53)	(52)
Preputial gland	(54)	(53)	(53)	(51)
Adenoma	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Carcinoma			1 (2%)	1 (2%)
Fibrous histiocytoma		1 (2%)		
Prostate	(53)	(53)	(53)	(52)
Adenoma			1 (2%)	
Seminal vesicle	(54)	(53)	(53)	(52)
Testes	(54)	(53)	(53)	(52)
Bilateral, interstitial cell, adenoma	20 (37%)	36 (68%)	27 (51%)	26 (50%)
Interstitial cell, adenoma	20 (37%)	10 (19%)	16 (30%)	21 (40%)
Hematopoietic System				
Bone marrow	(54)	(53)	(53)	(52)
Lymph node	(16)	(19)	(16)	(15)
Lymph node, bronchial	(52)	(51)	(53)	(52)
Lymph node, mandibular	(49)	(51)	(50)	(51)
Squamous cell carcinoma, metastatic			1 (2%)	
Lymph node, mesenteric	(54)	(53)	(53)	(51)
Lymph node, mediastinal	(47)	(52)	(52)	(52)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Hematopoietic System (continued)				
Spleen	(54)	(53)	(53)	(52)
Fibrosarcoma			1 (2%)	
Pheochromocytoma malignant, metastatic				1 (2%)
Thymus	(44)	(49)	(47)	(48)
Carcinoma, metastatic, lung				1 (2%)
Integumentary System				
Mammary gland	(54)	(53)	(53)	(52)
Fibroadenoma	2 (4%)		1 (2%)	
Skin	(13)	(4)	(14)	(6)
Basal cell adenoma	2 (15%)		1 (7%)	
Fibroma	3 (23%)	1 (25%)	1 (7%)	
Keratoacanthoma	1 (8%)	1 (25%)	1 (7%)	1 (17%)
Lipoma			1 (7%)	
Papilloma				1 (17%)
Squamous cell carcinoma		1 (25%)		
Squamous cell papilloma		1 (25%)	1 (7%)	
Trichoepithelioma			1 (7%)	
Scrotum, fibroma			1 (7%)	
Subcutaneous tissue, histiocytic sarcoma				1 (17%)
Subcutaneous tissue, neurofibrosarcoma	1 (8%)			
Subcutaneous tissue, sarcoma			1 (7%)	
Musculoskeletal System				
Bone	(54)	(53)	(53)	(52)
Pelvis, hemangiosarcoma		1 (2%)		
Skeletal muscle				(1)
Fibrous histiocytoma				1 (100%)
Nervous System				
Brain	(54)	(53)	(53)	(52)
Astrocytoma NOS			1 (2%)	
Granular cell tumor NOS		1 (2%)		
Peripheral nerve	(1)			(1)
Ganglion, paraganglioma benign	1 (100%)			1 (100%)
Respiratory System				
Lung	(54)	(53)	(53)	(52)
Alveolar/bronchiolar adenoma		1 (2%)	3 (6%)	2 (4%)
Alveolar/bronchiolar carcinoma			1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma, squamous differentiation			2 (4%)	
Fibrous histiocytoma, metastatic				1 (2%)
Histiocytic sarcoma, metastatic, skin				1 (2%)
Pheochromocytoma malignant, metastatic				1 (2%)
Squamous cell carcinoma	1 (2%)			
Nose	(54)	(53)	(53)	(52)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Special Senses System				
Ear			(1)	
Fibroma			1 (100%)	
Eye	(9)	(5)	(3)	(5)
Lids, fibroma		1 (20%)		
Harderian gland		(1)		
Carcinoma		1 (100%)		
Zymbal's gland	(1)			
Carcinoma	1 (100%)			
Urinary System				
Kidney	(54)	(53)	(53)	(52)
Histiocytic sarcoma, metastatic, skin				1 (2%)
Renal tubule, adenoma			1 (2%)	
Transitional epithelium, carcinoma			1 (2%)	
Urinary bladder	(54)	(53)	(53)	(52)
Systemic Lesions				
Multiple organs[b]	(54)	(53)	(53)	(52)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	31 (57%)	32 (60%)	26 (49%)	35 (67%)
Mesothelioma malignant		1 (2%)		2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	4	4	3	5
2-Year study	53	53	53	52
Total primary neoplasms				
15-Month interim evaluation	4	5	3	5
2-Year study	154	157	159	157
Total animals with benign neoplasms				
15-Month interim evaluation	4	4	3	5
2-Year study	52	51	52	52
Total benign neoplasms				
15-Month interim evaluation	4	5	3	5
2-Year study	114	117	116	105
Total animals with malignant neoplasms				
2-Year study	37	38	35	43
Total malignant neoplasms				
2-Year study	40	39	42	52

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Neoplasm Summary (continued)				
Total animals with metastatic neoplasms				
2-Year study		1	1	6
Total metastatic neoplasms				
2-Year study		3	1	19
Total animals with uncertain neoplasms-benign or malignant				
2-Year study		1	1	
Total uncertain neoplasms				
2-Year study		1	1	

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³

Number of Days on Study	1 8 7	4 7 5	5 0 3	5 0 9	5 2 4	5 6 6	5 6 6	5 6 9	5 7 3	5 7 3	5 8 1	5 8 4	5 8 5	5 9 4	5 9 8	6 2 2	6 2 2	6 2 2	6 2 2	6 2 4	6 2 4	6 2 8	6 2 8	6 2 9	6 5 6
Carcass ID Number	0 2 1	0 3 9	0 3 2	0 4 1	0 2 9	0 0 3	0 5 4	0 1 7	0 3 3	0 5 9	0 1 5	0 1 6	0 4 0	0 3 7	0 4 7	0 1 8	0 2 4	0 4 4	0 4 9	0 0 1	0 5 6	0 1 4	0 4 3	0 0 7	0 5 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																						X		X	
Hepatocellular adenoma		X															X								
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign		X			X						X								X						X
Bilateral, pheochromocytoma benign						X												X			X			X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Parathyroid gland	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X		X				X	X	X	X			X	X		X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma		X																							
C-cell, carcinoma																									
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
Tissue NOS								+					+			+									
Oral, osteosarcoma													X												
Genital System																									
Coagulating gland																+				+	+				
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³ (continued)

Number of Days on Study	6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	
	6 6 7 8 9 9 9 9 9 0 0 1 1 1 2 3 3 3 3 3 3 3 3 3 3 3 3 3	
	1 9 8 2 2 6 7 9 9 5 5 3 3 5 4 3 3 3 3 3 6 6 6 6 6 6 7 7 7	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Total
	4 0 5 4 3 1 1 3 3 0 5 3 4 2 5 0 0 0 2 6 0 1 2 4 6 6 1 5 6	Tissues/
	8 6 8 5 4 0 1 0 1 2 7 5 2 8 0 5 8 9 3 3 4 3 6 6 0 4 2 3 1	Tumors
Alimentary System		
Esophagus	+ +	54
Intestine large, colon	+ +	54
Intestine large, rectum	+ +	54
Intestine large, cecum	+ +	54
Intestine small, duodenum	+ +	54
Intestine small, jejunum	+ +	54
Intestine small, ileum	+ +	54
Liver	+ +	54
Hepatocellular carcinoma		2
Hepatocellular adenoma	X	3
Mesentery	+	1
Pancreas	+ +	54
Salivary glands	+ +	54
Stomach, forestomach	+ +	54
Stomach, glandular	+ +	54
Cardiovascular System		
Blood vessel	+ +	2
Heart	+ +	54
Endocrine System		
Adrenal cortex	+ +	54
Adrenal medulla	+ +	54
Pheochromocytoma benign	X X X X X X X X X X X X X	17
Bilateral, pheochromocytoma benign	X X X X X X	10
Islets, pancreatic	+ +	54
Adenoma	X X	2
Carcinoma	X	1
Parathyroid gland	+ + + + + + + + + M + + + + + + + + + + + + + + + + + +	50
Adenoma	X	1
Pituitary gland	+ M + + + + + +	53
Pars distalis, adenoma	X X X X X X X X X X X X X X X X X X X X X X X X	24
Thyroid gland	+ +	54
C-cell, adenoma	X X X X X X	6
C-cell, carcinoma	X	1
Follicular cell, adenoma	X	1
Follicular cell, carcinoma	X	1
General Body System		
Tissue NOS		3
Oral, osteosarcoma		1
Genital System		
Coagulating gland	+	4
Epididymis	+ +	54
Preputial gland	+ +	54
Adenoma	X	1
Prostate	+ +	53

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³ (continued)

Number of Days on Study	1 8 7	4 7 5	5 0 3	5 0 9	5 2 4	5 6 6	5 6 6	5 6 9	5 7 3	5 7 3	5 8 1	5 8 4	5 8 5	5 9 4	5 9 8	6 2 2	6 2 2	6 2 2	6 2 2	6 2 4	6 2 4	6 2 8	6 2 8	6 2 9	6 2 6
Carcass ID Number	0 2 1	0 3 9	0 3 2	0 4 1	0 2 9	0 0 3	0 5 4	0 1 7	0 3 3	0 5 9	0 1 5	0 1 6	0 4 0	0 3 7	0 4 7	0 1 8	0 2 4	0 4 4	0 4 9	0 0 1	0 5 6	0 1 4	0 4 3	0 0 7	0 5 2
Genital System (continued)																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma															X			X					X		X
Interstitial cell, adenoma				X		X	X				X	X	X			X	X		X			X		X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+		+			+			+					+					+		+	+
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	I	+	+	+	I	+	+	+	+	I	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin							+	+			+								+			+	+		+
Basal cell adenoma																									
Fibroma							X															X			
Keratoacanthoma								X																	
Subcutaneous tissue, neurofibrosarcoma																							X		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+																						
Ganglion, paraganglioma benign			X																						
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+		+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye				+	+	+					+	+			+										
Zymbal's gland					+																				
Carcinoma					X																				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X		X		X	X		X	X	X		X		X	X	X	X	X			X	X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³ (continued)

Number of Days on Study	6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	
	6 6 7 8 9 9 9 9 9 0 0 1 1 1 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3	
	1 9 8 2 2 6 7 9 9 5 5 3 3 5 4 3 3 3 3 6 6 6 6 6 6 7 7 7	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Total
	4 0 5 4 3 1 1 3 3 0 5 3 4 2 5 0 0 0 2 6 0 1 2 4 6 6 1 5 6	Tissues/
	8 6 8 5 4 0 1 0 1 2 7 5 2 8 0 5 8 9 3 3 4 3 6 6 0 4 2 3 1	Tumors
Genital System (continued)		
Seminal vesicle	+ +	54
Testes	+ +	54
Bilateral, interstitial cell, adenoma	X X X X X X X X X X	20
Interstitial cell, adenoma	X X X X X X X X	20
Hematopoietic System		
Bone marrow	+ +	54
Lymph node	+ + + + + + + + + + + + + + + +	16
Lymph node, bronchial	+ + + + + I + I +	52
Lymph node, mandibular	+ + + M + + + M + + M + + + + + + + + + + + + + + M + + +	49
Lymph node, mesenteric	+ +	54
Lymph node, mediastinal	+ + + + + + M + + I + M + + + M + + + + + + + + + + + + +	47
Spleen	+ +	54
Thymus	+ + M M + + M + + M + + + + + + + M + M + + + + + + + + +	44
Integumentary System		
Mammary gland	+ +	54
Fibroadenoma	X X	2
Skin	+ + + + + + + + + +	13
Basal cell adenoma	X X	2
Fibroma	X	3
Keratoacanthoma		1
Subcutaneous tissue, neurofibrosarcoma		1
Musculoskeletal System		
Bone	+ +	54
Nervous System		
Brain	+ +	54
Peripheral nerve		1
Ganglion, paraganglioma benign		1
Respiratory System		
Larynx	+ +	52
Lung	+ +	54
Squamous cell carcinoma	X	1
Nose	+ +	54
Trachea	+ +	53
Special Senses System		
Eye	+ + +	9
Zymbal's gland		1
Carcinoma		1
Urinary System		
Kidney	+ +	54
Urinary bladder	+ +	54
Systemic Lesions		
Multiple organs	+ +	54
Leukemia mononuclear	X X X X X X X X X X X X X X	31

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 0.62 mg/m³

Number of Days on Study	4 6 6	5 0 3	5 1 9	5 2 0	5 2 4	5 3 8	5 4 2	5 6 4	5 6 7	5 7 0	5 7 0	5 7 2	5 9 5	6 1 8	6 1 8	6 2 3	6 2 9	6 3 3	6 4 3	6 4 7	6 4 9	6 7 0	6 7 5	6 7 9	6 7 9
Carcass ID Number	1 4 5	1 6 0	1 4 9	1 6 5	1 6 6	1 8 4	1 7 9	1 3 9	1 5 7	1 4 6	1 8 9	1 7 4	1 4 7	1 5 3	1 7 2	1 5 0	1 7 0	1 5 6	1 4 2	1 4 1	1 7 6	1 8 1	1 4 8	1 6 7	1 9 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hepatocellular carcinoma																									
Hepatocellular adenoma																						X			
Hepatocellular adenoma, multiple																									
Mesentery					+																				
Mesothelioma malignant, metastatic					X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign											X	X		X			X				X	X			
Bilateral, pheochromocytoma benign													X		X									X	X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adenoma, multiple																									
Carcinoma																									
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X						X	X							X							X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																				X		X	X		
Follicular cell, adenoma																	X				X				
General Body System																									
Tissue NOS					+							+													
Mesothelioma malignant, metastatic					X																				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 0.62 mg/m³
(continued)

Number of Days on Study	6 8 5	6 8 6	6 9 6	6 9 7	6 9 7	7 0 0	7 0 3	7 0 4	7 0 9	7 1 2	7 1 7	7 1 7	7 2 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	
Carcass ID Number	1 4 0	1 3 6	1 7 7	1 3 3	1 8 2	1 6 9	1 4 3	1 5 8	1 3 2	1 9 2	1 6 8	1 7 1	1 5 2	1 3 8	1 5 1	1 6 1	1 7 3	1 7 8	1 8 6	1 8 8	1 9 4	1 5 5	1 6 4	1 7 5	1 8 0	1 8 5	1 8 7	1 9 0	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Fibroma		X																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hemangioma																										X		1
Hepatocellular carcinoma																		X										1
Hepatocellular adenoma		X	X											X												X		5
Hepatocellular adenoma, multiple	X																											1
Mesentery																												1
Mesothelioma malignant, metastatic																												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Cardiovascular System																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma																			X									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pheochromocytoma benign			X		X		X	X		X			X														X	13
Bilateral, pheochromocytoma benign		X										X				X	X					X		X		X		11
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma		X																				X						2
Adenoma, multiple													X															1
Carcinoma								X																				1
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pars distalis, adenoma		X	X		X					X	X				X	X	X		X		X			X	X		X		18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
C-cell, adenoma				X									X															5
Follicular cell, adenoma						X																						3
General Body System																												
Tissue NOS																												2
Mesothelioma malignant, metastatic																												1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 0.62 mg/m³
(continued)

Number of Days on Study	466	503	519	520	524	538	542	564	567	570	570	572	595	618	618	623	629	633	643	647	649	670	675	679	679
Carcass ID Number	145	160	149	165	166	184	179	139	157	146	189	174	147	153	172	150	170	156	142	141	176	181	148	167	193
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic					X																				
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X		X										
Fibrous histiocytoma	X																								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X	X					X	X	X	X		X			X	X	X		X	X	
Interstitial cell, adenoma	X			X			X								X			X				X			X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+		+		+					+		+	+	+				+	+	+				+
Lymph node, bronchial	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin										+		+													
Fibroma												X													
Keratoacanthoma										X															
Squamous cell carcinoma																									
Squamous cell papilloma										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, hemangiosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor NOS							X																		
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye															+				+						
Lids, fibroma																									
Harderian gland																								+	
Carcinoma																								X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 0.62 mg/m³
(continued)

Number of Days on Study	6 8 5	6 8 6	6 9 6	6 9 7	6 9 7	7 0 0	7 0 3	7 0 4	7 0 9	7 1 2	7 1 7	7 1 7	7 2 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 4 0	1 3 6	1 7 7	1 3 3	1 8 2	1 6 9	1 4 3	1 5 8	1 3 2	1 9 2	1 6 8	1 7 1	1 5 2	1 3 8	1 5 1	1 6 1	1 7 3	1 7 8	1 8 6	1 8 8	1 9 4	1 5 5	1 6 4	1 7 5	1 8 0	1 8 5	1 8 7	1 9 0	Total Tissues/ Tumors	
Genital System																														
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Mesothelioma malignant, metastatic																													1	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Adenoma																						X							3	
Fibrous histiocytoma																													1	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Bilateral, interstitial cell, adenoma			X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	36	
Interstitial cell, adenoma	X	X					X																						10	
Hematopoietic System																														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Lymph node		+	+			+				+		+	+	+								+							19	
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	49	
Integumentary System																														
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Skin							+					+																	4	
Fibroma																													1	
Keratoacanthoma																													1	
Squamous cell carcinoma							X																						1	
Squamous cell papilloma																													1	
Musculoskeletal System																														
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Pelvis, hemangiosarcoma										X																			1	
Nervous System																														
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Granular cell tumor NOS																													1	
Respiratory System																														
Larynx	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52	
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Alveolar/bronchiolar adenoma																													1	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Special Senses System																														
Eye			+			+		+																					5	
Lids, fibroma								X																					1	
Harderian gland																													1	
Carcinoma																													1	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 0.62 mg/m³
(continued)

Number of Days on Study	4	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6
	6	0	1	2	2	3	4	6	6	7	7	7	9	1	1	2	2	3	4	4	4	7	7	7	7
	6	3	9	0	4	8	2	4	7	0	0	2	5	8	8	3	9	3	3	7	9	0	5	9	9
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	4	6	4	6	6	8	7	3	5	4	8	7	4	5	7	5	7	5	4	4	7	8	4	6	9
	5	0	9	5	6	4	9	9	7	6	9	4	7	3	2	0	0	6	2	1	6	1	8	7	3
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X		X		X		X	X		X	X	X	X		X	X	X	X	X	X	X	X
Mesothelioma malignant					X																				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 0.62 mg/m³
(continued)

Number of Days on Study	6 8 5	6 8 6	6 9 6	6 9 7	6 9 7	7 0 0	7 0 3	7 0 4	7 0 9	7 1 2	7 1 7	7 1 7	7 2 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	
Carcass ID Number	1 4 0	1 3 6	1 7 7	1 3 3	1 8 2	1 6 9	1 4 3	1 5 8	1 3 2	1 9 2	1 6 8	1 7 1	1 5 2	1 3 8	1 5 1	1 6 1	1 7 3	1 7 8	1 8 6	1 8 8	1 9 4	1 5 5	1 6 4	1 7 5	1 8 0	1 8 5	1 8 7	1 9 0	Total Tissues/ Tumors
Urinary System																													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Systemic Lesions																													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear	X	X	X	X		X			X		X	X	X	X		X						X		X			X		32
Mesothelioma malignant																													1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³

Number of Days on Study	2 0 2	3 6 7	4 5 7	5 1 9	5 2 5	5 4 1	5 4 6	5 6 4	5 6 7	5 6 7	5 7 0	5 7 8	5 8 8	5 9 2	6 0 6	6 1 8	6 1 8	6 1 9	6 1 9	6 2 0	6 2 4	6 2 7	6 4 7	6 4 7	6 5 0
Carcass ID Number	2 6 7	3 1 1	3 2 4	3 2 3	2 9 0	3 1 9	3 2 2	2 8 3	2 9 7	3 1 8	3 0 8	3 1 2	2 8 2	2 8 1	2 7 5	2 6 9	2 9 2	2 6 3	2 9 5	3 0 4	3 0 0	2 7 4	2 9 8	3 2 1	2 8 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Anus, leiomyoma																								X	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular carcinoma, multiple								X																	
Hepatocellular adenoma										X									X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																								X	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell carcinoma																									
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																		X							
Pheochromocytoma benign				X									X			X				X					X
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma															X										
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X							X						X					X	X	X			
Pars intermedia, carcinoma																									
Thyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma															X										
Follicular cell, adenoma																									
General Body System																									
Tissue NOS																	+								
Lipoma																	X								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	6 7 4	6 7 6	6 8 1	6 8 1	6 9 0	6 9 0	6 9 7	7 0 6	7 0 6	7 0 6	7 0 7	7 1 7	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	
Carcass ID Number	2 8 0	3 1 6	3 1 0	3 2 5	2 7 0	2 9 9	2 8 7	2 6 5	2 7 3	2 8 9	3 0 3	2 7 9	2 6 4	2 6 1	2 6 8	2 7 8	2 8 5	2 8 8	2 9 3	2 9 6	3 1 4	2 9 1	2 6 2	2 6 6	3 0 5	3 0 7	3 0 9	3 1 3	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Anus, leiomyoma																													1
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hepatocellular carcinoma																		X											1
Hepatocellular carcinoma, multiple																													1
Hepatocellular adenoma						X																							3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Squamous cell carcinoma																													1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tongue											+																		1
Squamous cell carcinoma											X																		1
Cardiovascular System																													
Blood vessel													+																1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma malignant																													1
Pheochromocytoma benign					X			X	X	X	X					X			X	X	X	X	X			X			17
Bilateral, pheochromocytoma benign		X	X	X			X					X	X	X											X			X	9
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma										X																X			2
Carcinoma																											X		2
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	49
Adenoma												X																	1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	52
Pars distalis, adenoma	X	X		X						X	X					X		X	X		X					X			16
Pars intermedia, carcinoma														X															1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell, adenoma												X				X						X				X			4
C-cell, carcinoma																													1
Follicular cell, adenoma															X											X			2
General Body System																													
Tissue NOS																	+												2
Lipoma																	X												2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	2 0 2	3 6 7	4 5 7	5 1 9	5 2 5	5 4 1	5 4 6	5 6 4	5 6 7	5 6 7	5 7 0	5 7 8	5 8 8	5 8 2	6 0 6	6 1 8	6 1 8	6 1 9	6 1 9	6 2 0	6 2 4	6 2 7	6 4 7	6 4 7	6 5 0
Carcass ID Number	2 6 7	3 1 1	3 2 4	3 2 3	2 9 0	3 1 9	3 2 2	2 8 3	2 9 7	3 1 8	3 0 8	3 1 2	2 8 2	2 8 1	2 7 5	2 6 9	2 9 2	2 6 3	2 9 5	3 0 4	3 0 0	2 7 4	2 9 8	3 2 1	2 8 4
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Carcinoma												X													
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma								X				X	X		X	X	X	X					X	X	X
Interstitial cell, adenoma			X	X		X	X				X			X					X		X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+			+			+			+			+	+					+						+
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																								X	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin					+	+		+				+													
Basal cell adenoma																									
Fibroma					X																				
Keratoacanthoma																									
Lipoma																									
Squamous cell papilloma																									
Trichoepithelioma																									
Scrotum, fibroma						X																			
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma NOS																X									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	6 7 4	6 7 6	6 8 1	6 8 1	6 9 0	6 9 0	6 9 7	7 0 6	7 0 6	7 0 6	7 0 7	7 1 7	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	
Carcass ID Number	2 8 0	3 1 6	3 1 0	3 2 5	2 7 0	2 9 9	2 8 7	2 6 5	2 7 3	2 8 9	3 0 3	2 7 9	2 6 4	2 6 1	2 6 8	2 7 8	2 8 5	2 8 8	2 9 3	2 9 6	3 1 4	2 9 1	2 6 2	2 6 6	3 0 5	3 0 7	3 0 9	3 1 3	Total Tissues/ Tumors
Genital System																													
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma						X																							2
Carcinoma																													1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma		X																											1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Bilateral, interstitial cell, adenoma				X	X	X		X	X	X			X	X	X				X	X			X	X	X	X	X	X	27
Interstitial cell, adenoma			X				X					X				X	X	X			X	X							16
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node		+	+	+			+		+	+					+				+										16
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	50
Squamous cell carcinoma, metastatic																													1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	52
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Fibrosarcoma				X																									1
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	47
Integumentary System																													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Fibroadenoma				X																									1
Skin					+	+		+	+		+	+								+		+			+		+		14
Basal cell adenoma								X																					1
Fibroma																													1
Keratoacanthoma																									X				1
Lipoma												X																	1
Squamous cell papilloma					X																								1
Trichoepithelioma											X																		1
Scrotum, fibroma																													1
Subcutaneous tissue, sarcoma																				X									1
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Astrocytoma NOS																													1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	2	3	4	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6
	0	6	5	1	2	4	4	6	6	6	7	7	8	9	0	1	1	1	2	2	2	4	5
	2	7	7	9	5	1	6	4	7	7	0	8	8	2	6	8	8	9	0	4	7	7	0
Carcass ID Number	2	3	3	3	2	3	3	2	2	3	3	3	2	2	2	2	2	2	3	3	2	2	3	2
	6	1	2	2	9	1	2	8	9	1	0	1	8	8	7	6	9	6	9	0	0	7	9	2	8
	7	1	4	3	0	9	2	3	7	8	8	2	2	1	5	9	2	3	5	4	0	4	8	1	4
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma										X															
Alveolar/bronchiolar carcinoma, squamous differentiation																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear													+												
Fibroma													X												
Eye													+								+		+		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																						X			
Transitional epithelium, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X	X			X	X		X	X		X	X		X		X				X	X		X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	6 7 4	6 7 6	6 8 1	6 8 1	6 9 0	6 9 0	6 9 7	7 0 6	7 0 6	7 0 6	7 0 7	7 1 7	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	
Carcass ID Number	2 8 0	3 1 6	3 1 0	3 2 5	2 7 0	2 9 9	2 9 7	2 8 5	2 6 3	2 7 3	2 8 9	3 0 3	2 7 9	2 6 4	2 6 1	2 6 8	2 7 8	2 8 5	2 8 8	2 9 3	2 9 6	3 1 4	2 9 1	2 6 2	2 6 6	3 0 5	3 0 7	3 0 9	3 1 3	Total Tissues/ Tumors
Respiratory System																												
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Alveolar/bronchiolar adenoma																	X	X									X	3
Alveolar/bronchiolar carcinoma																												1
Alveolar/bronchiolar carcinoma, squamous differentiation	X					X																						2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																												
Ear																												1
Fibroma																												1
Eye																												3
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Renal tubule, adenoma																												1
Transitional epithelium, carcinoma				X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear		X	X	X	X		X	X	X	X		X			X							X				X		26

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³

Number of Days on Study	4 6 7	4 6 8	4 7 5	5 3 6	5 3 9	5 4 4	5 4 5	5 5 3	5 6 5	5 7 0	5 7 0	5 7 0	5 7 8	5 8 3	5 9 4	5 9 5	6 1 5	6 1 5	6 2 3	6 2 4	6 2 5	6 3 3	6 4 7
Carcass ID Number	4 0 5	4 1 2	4 5 1	4 0 0	4 0 2	4 4 6	4 4 2	4 0 8	4 4 9	4 1 6	4 1 8	4 3 5	4 4 0	4 3 8	4 3 9	4 0 7	4 3 7	4 4 3	4 3 0	4 4 4	3 4 9	4 1 9	4 3 6	4 5 3
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic	X																							
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic	X																							
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic	X																							
Intestine small, ileum		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic					X																			
Hepatocellular carcinoma																								
Hepatocellular adenoma																								
Histiocytic sarcoma, metastatic, skin															X									
Mesothelioma malignant, metastatic	X																							
Mesentery	+																							
Mesothelioma malignant, metastatic, testes	X																							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic	X																							
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes	X																							
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic	X																							
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung																								
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant	X															X								
Pheochromocytoma benign								X				X		X			X	X	X					X
Bilateral, pheochromocytoma benign											X												X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X																X	X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																								
Follicular cell, adenoma																								
Follicular cell, carcinoma																								X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	6 5 1	6 6 0	6 6 0	6 6 5	6 6 5	6 7 1	6 7 1	6 7 6	6 7 9	6 9 7	7 0 7	7 0 7	7 0 9	7 1 7	7 1 9	7 2 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	
Carcass ID Number	4 3 3	4 3 7	4 4 7	4 4 1	4 4 5	4 4 9	4 4 3	4 4 2	4 3 3	4 3 1	4 4 1	4 4 4	4 4 8	4 4 6	4 4 4	4 4 1	4 4 5	4 4 7	4 4 8	4 3 6	4 3 9	4 4 3	4 4 4	4 4 0	4 4 2	4 4 1	4 4 4	4 4 7	4 3 8	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Mesothelioma malignant, metastatic																													1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Mesothelioma malignant, metastatic																													1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Mesothelioma malignant, metastatic																													1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Fibrous histiocytoma, metastatic																													1
Hepatocellular carcinoma																								X					1
Hepatocellular adenoma					X																			X					2
Histiocytic sarcoma, metastatic, skin																													1
Mesothelioma malignant, metastatic																													1
Mesentery																													1
Mesothelioma malignant, metastatic, testes																													1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Mesothelioma malignant, metastatic																													1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Mesothelioma malignant, metastatic, testes																													1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Mesothelioma malignant, metastatic																													1
Cardiovascular System																													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, metastatic, lung										X																			1
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pheochromocytoma malignant																X		X			X						X		6
Pheochromocytoma benign						X		X			X			X		X			X		X					X	X		16
Bilateral, pheochromocytoma benign		X	X				X		X	X		X	X		X		X			X			X	X	X			X	16
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma						X				X																			2
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pars distalis, adenoma	X	X			X	X					X	X							X		X	X							12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell, adenoma										X																	X		2
Follicular cell, adenoma			X																										1
Follicular cell, carcinoma																													1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	4 6 7	4 6 8	4 7 5	5 3 6	5 3 9	5 4 4	5 4 5	5 5 3	5 6 5	5 7 0	5 7 0	5 7 0	5 7 8	5 8 3	5 8 4	5 9 5	6 1 5	6 1 5	6 2 3	6 2 4	6 2 5	6 2 5	6 3 3	6 4 7
Carcass ID Number	4 0 5	4 1 2	4 5 1	4 0 0	4 0 2	4 4 6	4 4 2	4 0 8	4 4 9	4 1 6	4 1 8	4 3 5	4 4 0	4 3 8	4 3 9	4 0 7	4 3 7	4 4 3	4 3 0	4 4 4	3 9 4	4 1 9	4 3 6	4 5 3
General Body System																								
Tissue NOS		+													+									
Basal cell carcinoma		X																						
Carcinoma, metastatic, lung																								
Fibrosarcoma															X									
Genital System																								
Coagulating gland																		+						
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																								
Preputial gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X	X												
Carcinoma			X																					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic	X																							
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X			X		X	X		X			X	X				X		X		X	X
Interstitial cell, adenoma	X	X		X	X		X			X		X				X	X	X		X				
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+				+				+				+	+	+			+			+			+
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, metastatic																X								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M
Carcinoma, metastatic, lung																								
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin								+						+	+				+					
Keratoacanthoma																								
Papilloma																								
Subcutaneous tissue, histiocytic sarcoma																X								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+																			
Fibrous histiocytoma					X																			
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																								
Ganglion, paraganglioma benign																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	6 5 1	6 6 0	6 6 0	6 6 5	6 6 5	6 7 1	6 7 1	6 7 6	6 7 9	6 9 7	7 0 7	7 0 7	7 0 9	7 1 7	7 1 9	7 2 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	
Carcass ID Number	4 3 3	3 9 7	4 1 7	4 1 1	4 2 5	4 0 9	4 1 3	4 2 2	3 9 3	3 9 1	4 0 1	4 2 4	4 2 8	4 2 6	4 5 4	4 3 1	4 1 5	4 2 7	4 4 8	3 9 6	3 9 9	3 0 3	4 0 4	4 2 0	4 2 1	4 3 4	4 4 7	3 9 8	Total Tissues/ Tumors
General Body System																													
Tissue NOS				+						+																			4
Basal cell carcinoma																													1
Carcinoma, metastatic, lung										X																			1
Fibrosarcoma																													1
Genital System																													
Coagulating gland																													1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Penis																									+				1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																													2
Carcinoma																													1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Mesothelioma malignant, metastatic																													1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Bilateral, interstitial cell, adenoma			X	X				X	X					X	X	X			X	X			X	X	X	X	X	X	26
Interstitial cell, adenoma		X			X	X	X			X			X				X	X			X	X							21
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node				+	+																+			+	+		+		15
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mandibular	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pheochromocytoma malignant, metastatic																													1
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, lung										X																			1
Integumentary System																													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Skin																			+									+	6
Keratoacanthoma																												X	1
Papilloma																			X										1
Subcutaneous tissue, histiocytic sarcoma																													1
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Skeletal muscle																													1
Fibrous histiocytoma																													1
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Peripheral nerve				+																									1
Ganglion, paraganglioma benign				X																									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	4 6 7	4 6 8	4 7 5	5 3 6	5 3 9	5 4 4	5 4 5	5 5 3	5 6 5	5 7 0	5 7 0	5 7 0	5 7 8	5 8 3	5 9 4	5 9 5	6 1 5	6 1 5	6 2 3	6 2 4	6 2 5	6 2 5	6 3 3	6 4 7
Carcass ID Number	4 0 5	4 1 2	4 5 1	4 0 0	4 0 2	4 4 6	4 4 2	4 0 8	4 4 9	4 1 6	4 1 8	4 3 5	4 4 0	4 3 8	4 3 9	4 0 7	4 3 7	4 4 3	4 3 0	4 4 4	3 4 4	4 9 4	4 1 9	4 3 6	4 5 3
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Alveolar/bronchiolar carcinoma																									
Fibrous histiocytoma, metastatic					X																				
Histiocytic sarcoma, metastatic, skin															X										
Pheochromocytoma malignant, metastatic																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+				+		+						+												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, skin															X										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Leukemia mononuclear				X	X		X	X	X	X		X	X	X		X	X	X	X	X				X	
Mesothelioma malignant	X																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	6 5 1	6 6 0	6 6 0	6 6 5	6 6 5	6 7 1	6 7 1	6 7 6	6 7 9	6 9 7	7 0 7	7 0 7	7 0 9	7 1 7	7 1 9	7 2 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	
Carcass ID Number	4 3 3	3 9 7	4 1 7	4 1 1	4 2 5	4 0 9	4 1 3	4 2 2	3 9 3	3 9 1	4 0 1	4 2 4	4 2 8	4 2 6	4 5 4	4 3 1	4 1 5	4 2 7	4 4 8	3 9 6	3 9 9	4 0 3	4 0 4	4 2 0	4 2 1	4 3 4	4 4 7	3 9 8	Total Tissues/ Tumors
Respiratory System																													
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar adenoma																												X	2
Alveolar/bronchiolar carcinoma										X									X										2
Fibrous histiocytoma, metastatic																													1
Histiocytic sarcoma, metastatic, skin																													1
Pheochromocytoma malignant, metastatic																		X											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Special Senses System																													
Eye																						+							5
Urinary System																													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma, metastatic, skin																													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Systemic Lesions																													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																													1
Leukemia mononuclear		X	X	X	X	X	X	X	X	X	X				X				X	X	X	X		X	X	X	X	X	35
Mesothelioma malignant																	X												2

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Oxide

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	27/54 (50%)	24/52 (46%)	26/53 (49%)	32/52 (62%)
Adjusted rate[b]	81.8%	69.3%	83.1%	93.8%
Terminal rate[c]	9/14 (64%)	6/15 (40%)	10/15 (67%)	10/12 (83%)
First incidence (days)	475	570	519	553
Life table test[d]	P=0.054	P=0.302N	P=0.472N	P=0.123
Logistic regression test[d]	P=0.041	P=0.348N	P=0.561N	P=0.095
Cochran-Armitage test[d]	P=0.094			
Fisher exact test[d]		P=0.420N	P=0.538N	P=0.159
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	0/54 (0%)	0/52 (0%)	1/53 (2%)	6/52 (12%)
Adjusted rate	0.0%	0.0%	2.8%	33.9%
Terminal rate	0/14 (0%)	0/15 (0%)	0/15 (0%)	3/12 (25%)
First incidence (days)	—[e]	—	619	467
Life table test	P<0.001	—	P=0.484	P=0.013
Logistic regression test	P<0.001	—	P=0.499	P=0.015
Cochran-Armitage test	P<0.001			
Fisher exact test		—	P=0.495	P=0.012
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	27/54 (50%)	24/52 (46%)	27/53 (51%)	35/52 (67%)
Adjusted rate	81.8%	69.3%	83.6%	97.0%
Terminal rate	9/14 (64%)	6/15 (40%)	10/15 (67%)	11/12 (92%)
First incidence (days)	475	570	519	467
Life table test	P=0.017	P=0.302N	P=0.537N	P=0.055
Logistic regression test	P=0.008	P=0.348N	P=0.521	P=0.027
Cochran-Armitage test	P=0.024			
Fisher exact test		P=0.420N	P=0.538	P=0.053
Liver: Hepatocellular Adenoma				
Overall rate	3/54 (6%)	6/53 (11%)	3/53 (6%)	2/52 (4%)
Adjusted rate	11.2%	25.0%	8.9%	12.0%
Terminal rate	1/14 (7%)	2/15 (13%)	0/15 (0%)	1/12 (8%)
First incidence (days)	475	670	567	665
Life table test	P=0.348N	P=0.283	P=0.634	P=0.555N
Logistic regression test	P=0.280N	P=0.245	P=0.660	P=0.517N
Cochran-Armitage test	P=0.271N			
Fisher exact test		P=0.235	P=0.652	P=0.518N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	5/54 (9%)	7/53 (13%)	5/53 (9%)	2/52 (4%)
Adjusted rate	16.7%	30.8%	16.8%	12.0%
Terminal rate	1/14 (7%)	3/15 (20%)	1/15 (7%)	1/12 (8%)
First incidence (days)	475	670	564	665
Life table test	P=0.185N	P=0.439	P=0.602	P=0.268N
Logistic regression test	P=0.134N	P=0.381	P=0.624	P=0.232N
Cochran-Armitage test	P=0.129N			
Fisher exact test		P=0.367	P=0.617	P=0.234N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	0/54 (0%)	1/53 (2%)	3/53 (6%)	2/52 (4%)
Adjusted rate	0.0%	2.6%	20.0%	11.4%
Terminal rate	0/14 (0%)	0/15 (0%)	3/15 (20%)	1/12 (8%)
First incidence (days)	—	623	733 (T)	633
Life table test	P=0.135	P=0.516	P=0.128	P=0.223
Logistic regression test	P=0.140	P=0.484	P=0.128	P=0.219
Cochran-Armitage test	P=0.165			
Fisher exact test		P=0.495	P=0.118	P=0.238
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	0/54 (0%)	0/53 (0%)	3/53 (6%)	2/52 (4%)
Adjusted rate	0.0%	0.0%	9.6%	13.2%
Terminal rate	0/14 (0%)	0/15 (0%)	0/15 (0%)	1/12 (8%)
First incidence (days)	—	—	567	697
Life table test	P=0.070	—	P=0.121	P=0.203
Logistic regression test	P=0.092	—	P=0.118	P=0.206
Cochran-Armitage test	P=0.098			
Fisher exact test		—	P=0.118	P=0.238
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	0/54 (0%)	1/53 (2%)	6/53 (11%)	4/52 (8%)
Adjusted rate	0.0%	2.6%	27.7%	23.7%
Terminal rate	0/14 (0%)	0/15 (0%)	3/15 (20%)	2/12 (17%)
First incidence (days)	—	623	567	633
Life table test	P=0.020	P=0.516	P=0.020	P=0.050
Logistic regression test	P=0.026	P=0.484	P=0.016	P=0.048
Cochran-Armitage test	P=0.034			
Fisher exact test		P=0.495	P=0.013	P=0.054
Lung: Alveolar/bronchiolar Adenoma or Carcinoma or Squamous Cell Carcinoma				
Overall rate	1/54 (2%)	1/53 (2%)	6/53 (11%)	4/52 (8%)
Adjusted rate	7.1%	2.6%	27.7%	23.7%
Terminal rate	1/14 (7%)	0/15 (0%)	3/15 (20%)	2/12 (17%)
First incidence (days)	733 (T)	623	567	633
Life table test	P=0.051	P=0.743N	P=0.065	P=0.143
Logistic regression test	P=0.062	P=0.760N	P=0.054	P=0.141
Cochran-Armitage test	P=0.079			
Fisher exact test		P=0.748	P=0.053	P=0.170
Pancreatic Islets: Adenoma				
Overall rate	2/54 (4%)	3/53 (6%)	2/53 (4%)	2/52 (4%)
Adjusted rate	11.8%	15.7%	11.1%	9.4%
Terminal rate	1/14 (7%)	1/15 (7%)	1/15 (7%)	0/12 (0%)
First incidence (days)	705	686	706	671
Life table test	P=0.591	P=0.525	P=0.662N	P=0.636
Logistic regression test	P=0.596N	P=0.533	P=0.696N	P=0.655
Cochran-Armitage test	P=0.541N			
Fisher exact test		P=0.491	P=0.684	P=0.677

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	3/54 (6%)	4/53 (8%)	4/53 (8%)	2/52 (4%)
Adjusted rate	18.6%	19.8%	19.6%	9.4%
Terminal rate	2/14 (14%)	1/15 (7%)	2/15 (13%)	0/12 (0%)
First incidence (days)	705	686	606	671
Life table test	P=0.446N	P=0.530	P=0.537	P=0.569N
Logistic regression test	P=0.434N	P=0.541	P=0.495	P=0.558N
Cochran-Armitage test	P=0.382N			
Fisher exact test		P=0.489	P=0.489	P=0.518N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	24/53 (45%)	18/52 (35%)	16/52 (31%)	12/52 (23%)
Adjusted rate	75.2%	67.3%	56.0%	47.8%
Terminal rate	7/13 (54%)	8/15 (53%)	5/14 (36%)	3/12 (25%)
First incidence (days)	569	519	367	539
Life table test	P=0.052N	P=0.127N	P=0.121N	P=0.052N
Logistic regression test	P=0.015N	P=0.124N	P=0.093N	P=0.015N
Cochran-Armitage test	P=0.012N			
Fisher exact test		P=0.180N	P=0.092N	P=0.014N
Preputial Gland: Adenoma				
Overall rate	1/54 (2%)	3/53 (6%)	2/53 (4%)	2/51 (4%)
Adjusted rate	5.0%	11.2%	6.4%	4.7%
Terminal rate	0/14 (0%)	1/15 (7%)	0/15 (0%)	0/12 (0%)
First incidence (days)	705	595	578	570
Life table test	P=0.455	P=0.319	P=0.496	P=0.472
Logistic regression test	P=0.487	P=0.303	P=0.492	P=0.471
Cochran-Armitage test	P=0.485			
Fisher exact test		P=0.302	P=0.493	P=0.478
Preputial Gland: Adenoma or Carcinoma				
Overall rate	1/54 (2%)	3/53 (6%)	2/53 (4%)	3/51 (6%)
Adjusted rate	5.0%	11.2%	6.4%	6.6%
Terminal rate	0/14 (0%)	1/15 (7%)	0/15 (0%)	0/12 (0%)
First incidence (days)	705	595	578	475
Life table test	P=0.262	P=0.319	P=0.496	P=0.282
Logistic regression test	P=0.283	P=0.303	P=0.492	P=0.249
Cochran-Armitage test	P=0.284			
Fisher exact test		P=0.302	P=0.493	P=0.288
Skin: Fibroma				
Overall rate	3/54 (6%)	1/53 (2%)	2/53 (4%)	0/52 (0%)
Adjusted rate	9.3%	2.4%	4.1%	0.0%
Terminal rate	0/14 (0%)	0/15 (0%)	0/15 (0%)	0/12 (0%)
First incidence (days)	566	572	525	—
Life table test	P=0.124N	P=0.310N	P=0.519N	P=0.150N
Logistic regression test	P=0.111N	P=0.337N	P=0.498N	P=0.127N
Cochran-Armitage test	P=0.110N			
Fisher exact test		P=0.316N	P=0.509N	P=0.129N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Skin: Papilloma, Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma, or Squamous Cell Carcinoma				
Overall rate	3/54 (6%)	2/53 (4%)	4/53 (8%)	2/52 (4%)
Adjusted rate	16.1%	6.7%	19.5%	16.7%
Terminal rate	2/14 (14%)	0/15 (0%)	1/15 (7%)	2/12 (17%)
First incidence (days)	569	570	690	733 (T)
Life table test	P=0.544N	P=0.489N	P=0.518	P=0.566N
Logistic regression test	P=0.532N	P=0.503N	P=0.490	P=0.552N
Cochran-Armitage test	P=0.494N			
Fisher exact test		P=0.509N	P=0.489	P=0.518N
Testes: Adenoma				
Overall rate	40/54 (74%)	46/53 (87%)	43/53 (81%)	47/52 (90%)
Adjusted rate	94.9%	100.0%	100.0%	100.0%
Terminal rate	12/14 (86%)	15/15 (100%)	15/15 (100%)	12/12 (100%)
First incidence (days)	509	466	457	467
Life table test	P=0.063	P=0.373	P=0.403	P=0.077
Logistic regression test	P=0.024	P=0.091	P=0.199	P=0.022
Cochran-Armitage test	P=0.039			
Fisher exact test		P=0.078	P=0.260	P=0.025
Thyroid Gland (C-cell): Adenoma				
Overall rate	6/54 (11%)	5/53 (9%)	4/52 (8%)	2/52 (4%)
Adjusted rate	28.1%	18.1%	24.7%	13.2%
Terminal rate	2/14 (14%)	0/15 (0%)	3/15 (20%)	1/12 (8%)
First incidence (days)	475	647	717	697
Life table test	P=0.143N	P=0.450N	P=0.339N	P=0.195N
Logistic regression test	P=0.120N	P=0.491N	P=0.382N	P=0.161N
Cochran-Armitage test	P=0.104N			
Fisher exact test		P=0.513N	P=0.395N	P=0.148N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	7/54 (13%)	5/53 (9%)	5/52 (10%)	2/52 (4%)
Adjusted rate	32.6%	18.1%	26.6%	13.2%
Terminal rate	2/14 (14%)	0/15 (0%)	3/15 (20%)	1/12 (8%)
First incidence (days)	475	647	606	697
Life table test	P=0.108N	P=0.334N	P=0.350N	P=0.128N
Logistic regression test	P=0.087N	P=0.367N	P=0.398N	P=0.102N
Cochran-Armitage test	P=0.075N			
Fisher exact test		P=0.394N	P=0.407N	P=0.090N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	1/54 (2%)	3/53 (6%)	2/52 (4%)	1/52 (2%)
Adjusted rate	4.5%	9.8%	13.3%	3.7%
Terminal rate	0/14 (0%)	0/15 (0%)	2/15 (13%)	0/12 (0%)
First incidence (days)	699	629	733 (T)	660
Life table test	P=0.529N	P=0.349	P=0.511	P=0.730
Logistic regression test	P=0.509N	P=0.306	P=0.505	P=0.746
Cochran-Armitage test	P=0.485N			
Fisher exact test		P=0.302	P=0.486	P=0.743

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	2/54 (4%)	3/53 (6%)	2/52 (4%)	2/52 (4%)
Adjusted rate	9.8%	9.8%	13.3%	7.0%
Terminal rate	0/14 (0%)	0/15 (0%)	2/15 (13%)	0/12 (0%)
First incidence (days)	699	629	733 (T)	647
Life table test	P=0.590N	P=0.541	P=0.690N	P=0.648
Logistic regression test	P=0.569N	P=0.507	P=0.696N	P=0.668
Cochran-Armitage test	P=0.542N			
Fisher exact test		P=0.491	P=0.677	P=0.677
All Organs: Mononuclear Cell Leukemia				
Overall rate	31/54 (57%)	32/53 (60%)	26/53 (49%)	35/52 (67%)
Adjusted rate	77.2%	73.3%	63.1%	90.1%
Terminal rate	7/14 (50%)	5/15 (33%)	3/15 (20%)	9/12 (75%)
First incidence (days)	475	503	202	536
Life table test	P=0.155	P=0.521N	P=0.309N	P=0.173
Logistic regression test	P=0.211	P=0.419	P=0.245N	P=0.212
Cochran-Armitage test	P=0.207			
Fisher exact test		P=0.454	P=0.251N	P=0.198
All Organs: Benign Neoplasms				
Overall rate	53/54 (98%)	51/53 (96%)	52/53 (98%)	52/52 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	14/14 (100%)	15/15 (100%)	15/15 (100%)	12/12 (100%)
First incidence (days)	187	466	367	467
Life table test	P=0.227	P=0.337N	P=0.507N	P=0.320
Logistic regression test	P=0.303	P=0.390N	P=0.777	P=0.530
Cochran-Armitage test	P=0.255			
Fisher exact test		P=0.493N	P=0.748N	P=0.509
All Organs: Malignant Neoplasms				
Overall rate	37/54 (69%)	38/53 (72%)	35/53 (66%)	43/52 (83%)
Adjusted rate	84.1%	80.1%	77.9%	97.3%
Terminal rate	8/14 (57%)	6/15 (40%)	6/15 (40%)	11/12 (92%)
First incidence (days)	475	466	202	467
Life table test	P=0.089	P=0.504N	P=0.465N	P=0.116
Logistic regression test	P=0.071	P=0.434	P=0.472N	P=0.071
Cochran-Armitage test	P=0.068			
Fisher exact test		P=0.441	P=0.473N	P=0.070

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
All Organs: Benign or Malignant Neoplasms				
Overall rate	54/54 (100%)	53/53 (100%)	53/53 (100%)	52/52 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	14/14 (100%)	15/15 (100%)	15/15 (100%)	12/12 (100%)
First incidence (days)	187	466	202	467
Life table test	P=0.281	P=0.386N	P=0.509N	P=0.359
Logistic regression test	—[f]	—	—	—
Cochran-Armitage test	—			
Fisher exact test		P=1.000N	P=1.000N	P=1.000N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A4a
Historical Incidence of Lung Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls			
	Alveolar/bronchiolar Adenoma	Alveolar/bronchiolar Carcinoma	Squamous Cell Carcinoma	Alveolar/bronchiolar Adenoma or Carcinoma or Squamous Cell Carcinoma
Historical Incidence at Lovelace Inhalation Toxicology Research Institute				
Nickel Oxide	0/54	0/54	1/54	1/54
Nickel Subsulfide	0/53	0/53	0/53	0/53
Nickel Sulfate Hexahydrate	0/54	1/54	1/54	2/54
Talc[b]	0/49	0/49	0/49	0/49
Overall Historical Incidence in Inhalation Studies				
Total	17/703 (2.4%)	6/703 (0.9%)	4/703 (0.6%)	27/703 (3.8%)
Standard deviation	3.5%	1.0%	0.9%	3.8%
Range	0%-10%	0%-2%	0%-2%	0%-10%
Overall Historical Incidence in Feed Studies				
Total	28/1,200 (2.3%)	11/1,200 (0.9%)	0/1,200 (0%)	39/1,200 (3.3%)
Standard deviation	2.0%	1.2%		2.0%
Range	0%-6%	0%-4%		0%-8%

[a] Data as of 17 June 1994
[b] Results of lifetime study; others are 2-year studies

TABLE A4b
Historical Incidence of Pheochromocytomas of the Adrenal Medulla in Untreated Male F344/N Rats[a]

Study	Incidence in Controls				
	Benign	Complex	Malignant	NOS	Benign, Complex, Malignant or NOS
Historical Incidence at Lovelace Inhalation Toxicology Research Institute[b]					
Nickel Oxide	27/54	0/54	0/54	0/54	27/54
Nickel Subsulfide	13/53	1/53	0/53	0/53	14/53
Nickel Sulfate Hexahydrate	16/54	0/54	0/54	0/54	16/54
Overall Historical Incidence in Inhalation Studies					
Total	163/623 (26.2%)	2/623 (0.3%)	11/623 (1.8%)	7/623 (1.1%)	176/623 (28.3%)
Standard deviation	13.1%	0.8%	2.9%	3.9%	12.0%
Range	0%-50%	0%-2%	0%-10%	0%-14%	8%-50%
Overall Historical Incidence in Feed Studies					
Total	379/1,182 (32.1%)	2/1,182 (0.2%)	33/1,182 (2.8%)	0/1,182 (0%)	400/1,182 (33.8%)
Standard deviation	11.7%	0.6%	3.2%		10.9%
Range	10%-63%	0%-2%	0%-12%		14%-63%

[a] Data as of 17 June 1994
[b] Talc excluded because it was not a 2-year study.

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Disposition Summary				
Animals initially in study	65	65	65	65
7-Month interim evaluation	6	7	7	7
15-Month interim evaluation	5	5	5	5
Early deaths				
Moribund	39	35	32	36
Natural deaths	1	3	6	4
Survivors				
Died last week of study			1	1
Terminal sacrifice	14	15	14	11
Missexed				1
Animals examined microscopically	65	65	65	64
7-Month Interim Evaluation				
Alimentary System				
Liver			(1)	
Hepatodiaphragmatic nodule			1 (100%)	
Hematopoietic System				
Lymph node			(1)	
Pigmentation			1 (100%)	
Lymph node, bronchial	(6)	(7)	(7)	(7)
Congestion, chronic	1 (17%)			
Hyperplasia				1 (14%)
Hyperplasia, lymphoid	1 (17%)		7 (100%)	4 (57%)
Pigmentation			7 (100%)	7 (100%)
Lymph node, mediastinal	(6)	(6)	(6)	(6)
Congestion		1 (17%)		
Hyperplasia, lymphoid			3 (50%)	
Pigmentation			4 (67%)	3 (50%)
Respiratory System				
Lung	(6)	(7)	(7)	(7)
Inflammation, chronic	3 (50%)		7 (100%)	7 (100%)
Alveolus, pigmentation		6 (86%)	7 (100%)	6 (86%)
Urinary System				
Urinary bladder	(3)	(3)	(5)	(4)
Calculus, microscopic observation only	3 (100%)	3 (100%)	5 (100%)	4 (100%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
7-Month Interim Evaluation (continued)				
Systems Examined With No Lesions Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
15-Month Interim Evaluation				
Alimentary System				
Liver	(5)	(5)	(5)	(5)
Eosinophilic focus			1 (20%)	
Hepatocyte, hyperplasia				1 (20%)
Endocrine System				
Adrenal medulla	(5)	(5)	(5)	(5)
Hyperplasia			1 (20%)	2 (40%)
Pituitary gland	(5)	(5)	(5)	(5)
Hyperplasia				1 (20%)
Genital System				
Preputial gland	(5)	(5)	(5)	(5)
Inflammation, suppurative				1 (20%)
Duct, ectasia		1 (20%)		
Testes	(5)	(5)	(5)	(5)
Interstitial cell, hyperplasia	1 (20%)	1 (20%)	3 (60%)	
Hematopoietic System				
Bone marrow	(5)	(5)	(5)	(5)
Hyperplasia				1 (20%)
Lymph node, bronchial	(5)	(5)	(5)	(5)
Hyperplasia, lymphoid			4 (80%)	4 (80%)
Pigmentation		5 (100%)	5 (100%)	5 (100%)
Lymph node, mediastinal	(5)	(5)	(5)	(4)
Hyperplasia, lymphoid			2 (40%)	1 (25%)
Pigmentation		3 (60%)	4 (80%)	4 (100%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(5)	(5)	(5)	(5)
Inflammation, chronic	4 (80%)	5 (100%)	5 (100%)	5 (100%)
Alveolus, pigmentation		5 (100%)	5 (100%)	5 (100%)
Nose	(5)	(5)	(5)	(5)
Respiratory epithelium, inflammation, focal, suppurative	1 (20%)			
Special Senses System				
Eye	(3)			
Cataract	1 (33%)			
Cornea, edema	1 (33%)			
Retina, degeneration	1 (33%)			
Vitreous, inflammation, chronic	1 (33%)			
Urinary System				
Kidney	(5)	(5)	(5)	(5)
Nephropathy	5 (100%)	4 (80%)	5 (100%)	4 (80%)
Urinary bladder	(5)	(5)	(5)	(5)
Calculus, microscopic observation only	3 (60%)	1 (20%)	1 (20%)	
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
2-Year Study				
Alimentary System				
Intestine large, colon	(54)	(53)	(53)	(52)
Erosion		1 (2%)		
Parasite metazoan	1 (2%)		1 (2%)	1 (2%)
Intestine large, rectum	(54)	(53)	(52)	(52)
Parasite metazoan	1 (2%)	1 (2%)		
Intestine large, cecum	(54)	(53)	(52)	(51)
Inflammation, chronic active		1 (2%)		
Inflammation, suppurative			1 (2%)	
Necrosis			1 (2%)	
Parasite metazoan			1 (2%)	
Ulcer			1 (2%)	
Intestine small, jejunum	(54)	(53)	(53)	(52)
Inflammation, chronic			1 (2%)	
Inflammation, chronic active				1 (2%)
Inflammation, suppurative		1 (2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(54)	(53)	(53)	(52)
Angiectasis			1 (2%)	
Basophilic focus	21 (39%)	15 (28%)	22 (42%)	20 (38%)
Clear cell focus	1 (2%)	1 (2%)		
Congestion			1 (2%)	4 (8%)
Degeneration, cystic	16 (30%)	20 (38%)	27 (51%)	28 (54%)
Developmental malformation		1 (2%)		1 (2%)
Eosinophilic focus	3 (6%)	4 (8%)	5 (9%)	7 (13%)
Fatty change	13 (24%)	15 (28%)	20 (38%)	11 (21%)
Hemorrhage				1 (2%)
Hepatodiaphragmatic nodule	4 (7%)	1 (2%)	2 (4%)	4 (8%)
Infarct				1 (2%)
Inflammation, chronic active			1 (2%)	
Inflammation, suppurative	1 (2%)			
Mixed cell focus				1 (2%)
Pigmentation, bile	1 (2%)		1 (2%)	
Thrombosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Thrombosis, multiple	2 (4%)			
Bile duct, hyperplasia	17 (31%)	20 (38%)	18 (34%)	25 (48%)
Hepatocyte, hyperplasia	8 (15%)	14 (26%)	9 (17%)	10 (19%)
Hepatocyte, necrosis	8 (15%)	14 (26%)	4 (8%)	10 (19%)
Portal vein, thrombosis				1 (2%)
Pancreas	(54)	(53)	(53)	(52)
Atrophy	1 (2%)	1 (2%)		
Congestion				1 (2%)
Fibrosis			1 (2%)	
Acinus, atrophy	5 (9%)	1 (2%)	1 (2%)	2 (4%)
Acinus, fibrosis	1 (2%)			
Acinus, hyperplasia	2 (4%)	1 (2%)		
Stomach, forestomach	(54)	(53)	(53)	(52)
Edema	3 (6%)			
Hyperkeratosis		1 (2%)	6 (11%)	1 (2%)
Inflammation, acute			1 (2%)	
Inflammation, chronic		1 (2%)	3 (6%)	
Inflammation, chronic active			1 (2%)	
Inflammation, suppurative	1 (2%)			
Ulcer	1 (2%)	3 (6%)	3 (6%)	
Ulcer, multiple	2 (4%)			
Stomach, glandular	(54)	(53)	(53)	(52)
Erosion		1 (2%)	1 (2%)	
Inflammation, chronic		1 (2%)		1 (2%)
Inflammation, chronic active		1 (2%)		
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)	
Pigmentation			1 (2%)	
Ulcer	1 (2%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Cardiovascular System				
Blood vessel	(2)		(1)	
Aorta, mineralization	2 (100%)		1 (100%)	
Heart	(54)	(53)	(53)	(52)
Fibrosis		1 (2%)		
Infarct				1 (2%)
Inflammation, chronic			1 (2%)	1 (2%)
Inflammation, suppurative	2 (4%)			
Atrium, congestion				1 (2%)
Atrium, thrombosis	4 (7%)	6 (11%)	4 (8%)	4 (8%)
Epicardium, degeneration		1 (2%)		
Myocardium, mineralization	1 (2%)			
Ventricle, fibrosis				1 (2%)
Ventricle, inflammation, chronic				1 (2%)
Ventricle, mineralization				1 (2%)
Ventricle, thrombosis				1 (2%)
Endocrine System				
Adrenal cortex	(54)	(53)	(53)	(52)
Angiectasis		2 (4%)		
Degeneration, fatty	2 (4%)	1 (2%)	6 (11%)	3 (6%)
Adrenal medulla	(54)	(52)	(53)	(52)
Cyst		1 (2%)		
Degeneration, fatty	1 (2%)			
Hyperplasia	25 (46%)	27 (52%)	26 (49%)	24 (46%)
Islets, pancreatic	(54)	(53)	(53)	(52)
Hyperplasia		3 (6%)	2 (4%)	1 (2%)
Parathyroid gland	(50)	(50)	(49)	(49)
Hyperplasia	2 (4%)		2 (4%)	2 (4%)
Pituitary gland	(53)	(52)	(52)	(52)
Angiectasis	2 (4%)	3 (6%)		
Hyperplasia		1 (2%)		
Pars distalis, angiectasis		1 (2%)		3 (6%)
Pars distalis, cyst	2 (4%)			2 (4%)
Pars distalis, hyperplasia	4 (8%)	3 (6%)	6 (12%)	11 (21%)
Pars distalis, necrosis		1 (2%)		
Pars distalis, pigmentation			1 (2%)	
Thyroid gland	(54)	(53)	(52)	(52)
Hyperplasia, cystic			1 (2%)	
Infiltration cellular, lymphocyte			1 (2%)	
C-cell, hyperplasia	1 (2%)	1 (2%)	2 (4%)	2 (4%)
General Body System				
Tissue NOS	(3)	(2)	(2)	(4)
Developmental malformation		1 (50%)		
Oral, inflammation, chronic active	1 (33%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Genital System				
Coagulating gland	(4)			(1)
Inflammation, chronic	1 (25%)			
Inflammation, suppurative	2 (50%)			1 (100%)
Epididymis	(54)	(53)	(53)	(52)
Spermatocele	1 (2%)		2 (4%)	
Preputial gland	(54)	(53)	(53)	(51)
Ectasia	2 (4%)	3 (6%)	4 (8%)	1 (2%)
Hyperplasia, glandular				1 (2%)
Inflammation, suppurative	3 (6%)	1 (2%)		2 (4%)
Bilateral, ectasia		1 (2%)		
Prostate	(53)	(53)	(53)	(52)
Hyperplasia			1 (2%)	
Inflammation, chronic	3 (6%)	3 (6%)		1 (2%)
Inflammation, chronic active		1 (2%)	1 (2%)	1 (2%)
Inflammation, suppurative	3 (6%)	1 (2%)	4 (8%)	
Seminal vesicle	(54)	(53)	(53)	(52)
Atrophy	3 (6%)		3 (6%)	
Ectasia	1 (2%)		1 (2%)	
Inflammation, suppurative			2 (4%)	
Testes	(54)	(53)	(53)	(52)
Atrophy	11 (20%)	7 (13%)	7 (13%)	10 (19%)
Hemorrhage			1 (2%)	
Bilateral, atrophy		1 (2%)	2 (4%)	
Interstitial cell, hyperplasia	7 (13%)	3 (6%)		
Hematopoietic System				
Bone marrow	(54)	(53)	(53)	(52)
Fibrosis	7 (13%)	4 (8%)	5 (9%)	4 (8%)
Hyperplasia	24 (44%)	35 (66%)	19 (36%)	35 (67%)
Lymph node	(16)	(19)	(16)	(15)
Hyperplasia, macrophage				1 (7%)
Pigmentation		4 (21%)		
Iliac, congestion		2 (11%)		
Iliac, ectasia			1 (6%)	
Iliac, hyperplasia, lymphoid	1 (6%)	1 (5%)	1 (6%)	
Iliac, pigmentation			1 (6%)	1 (7%)
Pancreatic, congestion		1 (5%)		
Pancreatic, hyperplasia, lymphoid	1 (6%)			
Renal, congestion		2 (11%)	1 (6%)	
Renal, edema				1 (7%)
Renal, hyperplasia, lymphoid	1 (6%)	2 (11%)	1 (6%)	
Renal, pigmentation		3 (16%)		2 (13%)
Lymph node, bronchial	(52)	(51)	(53)	(52)
Congestion	1 (2%)	1 (2%)		3 (6%)
Edema		1 (2%)		1 (2%)
Hyperplasia, lymphoid		7 (14%)	10 (19%)	18 (35%)
Hyperplasia, macrophage	1 (2%)			
Pigmentation		45 (88%)	51 (96%)	51 (98%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(49)	(51)	(50)	(51)
Hyperplasia, lymphoid	5 (10%)	4 (8%)	6 (12%)	3 (6%)
Lymph node, mesenteric	(54)	(53)	(53)	(51)
Congestion		2 (4%)		
Edema		1 (2%)		
Hyperplasia		1 (2%)		
Hyperplasia, lymphoid	1 (2%)	2 (4%)		1 (2%)
Lymph node, mediastinal	(47)	(52)	(52)	(52)
Congestion	1 (2%)	2 (4%)		3 (6%)
Ectasia	1 (2%)		1 (2%)	
Hyperplasia, lymphoid	5 (11%)	8 (15%)	11 (21%)	18 (35%)
Hyperplasia, plasma cell	3 (6%)	2 (4%)		1 (2%)
Pigmentation		33 (63%)	43 (83%)	50 (96%)
Spleen	(54)	(53)	(53)	(52)
Congestion			1 (2%)	
Developmental malformation	1 (2%)		1 (2%)	
Fibrosis	11 (20%)	7 (13%)	15 (28%)	10 (19%)
Infarct	4 (7%)	6 (11%)	3 (6%)	2 (4%)
Necrosis		1 (2%)	1 (2%)	
Capsule, fibrosis			1 (2%)	
Thymus	(44)	(49)	(47)	(48)
Congestion				1 (2%)
Integumentary System				
Mammary gland	(54)	(53)	(53)	(52)
Ectasia				1 (2%)
Hyperplasia	1 (2%)			
Duct, ectasia		1 (2%)		
Skin	(13)	(4)	(14)	(6)
Alopecia			1 (7%)	
Cyst epithelial inclusion	2 (15%)	2 (50%)	2 (14%)	1 (17%)
Hyperkeratosis	1 (8%)		1 (7%)	
Necrosis			1 (7%)	
Pigmentation	1 (8%)			1 (17%)
Epidermis, hyperplasia			1 (7%)	
Musculoskeletal System				
Bone	(54)	(53)	(53)	(52)
Hyperostosis		1 (2%)	2 (4%)	2 (4%)
Femur, hyperostosis		2 (4%)		4 (8%)
Nervous System				
Brain	(54)	(53)	(53)	(52)
Hemorrhage				1 (2%)
Cerebellum, compression		1 (2%)	1 (2%)	1 (2%)
Cerebellum, hemorrhage		2 (4%)	3 (6%)	
Cerebellum, ventricle, dilatation			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Nervous System (continued)				
Brain (continued)	(54)	(53)	(53)	(52)
Cerebrum, compression		5 (9%)	7 (13%)	5 (10%)
Cerebrum, degeneration	1 (2%)			
Cerebrum, hemorrhage		1 (2%)	1 (2%)	
Cerebrum, necrosis	1 (2%)			1 (2%)
Cerebrum, ventricle, dilatation			2 (4%)	3 (6%)
Hypothalamus, compression	8 (15%)		1 (2%)	
Pons, compression	2 (4%)			
Thalamus, degeneration	1 (2%)			
Ventricle, dilatation	2 (4%)	1 (2%)	1 (2%)	
Respiratory System				
Larynx	(52)	(52)	(53)	(51)
Inflammation, chronic	2 (4%)			1 (2%)
Inflammation, chronic active				2 (4%)
Inflammation, suppurative	1 (2%)			
Lung	(54)	(53)	(53)	(52)
Congestion				1 (2%)
Cyst				1 (2%)
Hemorrhage		1 (2%)	1 (2%)	2 (4%)
Inflammation, chronic	28 (52%)	53 (100%)	53 (100%)	52 (100%)
Mineralization	1 (2%)			
Alveolar epithelium, hyperplasia, atypical			4 (8%)	3 (6%)
Alveolar epithelium, hyperplasia, focal		2 (4%)	1 (2%)	
Alveolar epithelium, metaplasia, squamous		1 (2%)		
Alveolus, pigmentation	1 (2%)	53 (100%)	53 (100%)	52 (100%)
Nose	(54)	(53)	(53)	(52)
Inflammation, chronic active	1 (2%)	2 (4%)	2 (4%)	5 (10%)
Inflammation, suppurative	5 (9%)	2 (4%)	3 (6%)	2 (4%)
Trachea	(53)	(53)	(53)	(52)
Inflammation, focal, suppurative	1 (2%)			
Special Senses System				
Eye	(9)	(5)	(3)	(5)
Cataract	4 (44%)	3 (60%)	1 (33%)	3 (60%)
Anterior chamber, cornea, inflammation, suppurative	1 (11%)			
Bilateral, cornea, edema	1 (11%)			
Cornea, edema	1 (11%)			
Cornea, inflammation, suppurative		1 (20%)		
Lids, inflammation, chronic active		1 (20%)		
Sclera, metaplasia, osseous	1 (11%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m^3	0.62 mg/m^3	1.25 mg/m^3	2.5 mg/m^3
2-Year Study (continued)				
Urinary System				
Kidney	(54)	(53)	(53)	(52)
Cyst	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Fibrosis				1 (2%)
Infarct		1 (2%)		2 (4%)
Necrosis			1 (2%)	
Nephropathy	47 (87%)	50 (94%)	48 (91%)	43 (83%)
Pigmentation		1 (2%)		
Bilateral, nephropathy	1 (2%)			
Bilateral, cortex, cyst		1 (2%)		
Cortex, cyst	2 (4%)			1 (2%)
Medulla, congestion				1 (2%)
Medulla, cyst			1 (2%)	
Pelvis, degeneration			1 (2%)	
Pelvis, inflammation, suppurative			1 (2%)	
Urinary bladder	(54)	(53)	(53)	(52)
Calculus, microscopic observation only	2 (4%)	1 (2%)	3 (6%)	
Inflammation, subacute	1 (2%)			
Metaplasia, squamous			1 (2%)	

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF NICKEL OXIDE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Disposition Summary				
Animals initially in study	65	65	65	65
7-Month interim evaluation	7	7	7	6
15-Month interim evaluation	5	5	5	5
Early deaths				
Moribund	27	24	27	25
Natural deaths	5	3	6	3
Survivors				
Terminal sacrifice	21	26	20	26
Animals examined microscopically	65	65	65	65
7-Month Interim Evaluation				
Alimentary System				
Mesentery			(1)	
Lipoma			1 (100%)	
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
15-Month Interim Evaluation				
Endocrine System				
Pituitary gland	(5)	(5)	(5)	(5)
Pars distalis, adenoma	1 (20%)	3 (60%)		1 (20%)
Pars intermedia, adenoma				1 (20%)
Thyroid gland	(5)	(5)	(5)	(5)
C-cell, adenoma	1 (20%)	1 (20%)		
Genital System				
Uterus	(5)	(5)	(5)	(5)
Polyp stromal			2 (40%)	1 (20%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Esophagus	(52)	(53)	(53)	(54)
Lipoma				1 (2%)
Sarcoma, metastatic			1 (2%)	
Liver	(53)	(53)	(53)	(54)
Hepatocellular adenoma		1 (2%)		1 (2%)
Sarcoma, metastatic			1 (2%)	
Mesentery				(1)
Lipoma				1 (100%)
Pancreas	(52)	(53)	(53)	(54)
Salivary glands	(52)	(52)	(51)	(53)
Osteosarcoma, metastatic		1 (2%)		
Parotid gland, adenoma				1 (2%)
Stomach, forestomach	(52)	(53)	(53)	(54)
Tooth	(1)			(1)
Odontoma	1 (100%)			
Cardiovascular System				
Blood vessel	(3)	(1)	(2)	
Heart	(53)	(53)	(53)	(54)
Osteosarcoma, metastatic		1 (2%)		
Endocrine System				
Adrenal cortex	(53)	(53)	(53)	(54)
Carcinoma	1 (2%)			
Adrenal medulla	(51)	(52)	(53)	(53)
Pheochromocytoma benign	3 (6%)	7 (13%)	5 (9%)	13 (25%)
Bilateral, pheochromocytoma benign	1 (2%)		1 (2%)	5 (9%)
Islets, pancreatic	(52)	(53)	(53)	(54)
Adenoma	1 (2%)	1 (2%)	1 (2%)	
Osteosarcoma, metastatic		1 (2%)		
Pituitary gland	(52)	(52)	(52)	(54)
Pars distalis, adenoma	20 (38%)	21 (40%)	19 (37%)	20 (37%)
Pars distalis, carcinoma	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Thyroid gland	(52)	(52)	(53)	(53)
C-cell, adenoma	1 (2%)	1 (2%)	3 (6%)	2 (4%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
General Body System				
Tissue NOS	(6)	(1)	(3)	(3)
Fibroma				1 (33%)
Fibrosarcoma	1 (17%)			
Fibrous histiocytoma		1 (100%)		
Lipoma			2 (67%)	
Liposarcoma			1 (33%)	
Osteosarcoma	1 (17%)			
Squamous cell carcinoma	2 (33%)			
Oral, squamous cell carcinoma	1 (17%)			
Genital System				
Clitoral gland	(53)	(53)	(51)	(50)
Adenoma	1 (2%)	4 (8%)	1 (2%)	
Carcinoma	2 (4%)			1 (2%)
Bilateral, adenoma		1 (2%)	1 (2%)	
Ovary	(53)	(53)	(53)	(54)
Granulosa-theca tumor benign	1 (2%)			
Uterus	(53)	(53)	(52)	(54)
Polyp stromal	9 (17%)	2 (4%)	6 (12%)	5 (9%)
Schwannoma malignant				1 (2%)
Vagina	(2)	(1)	(1)	
Polyp	1 (50%)			
Hematopoietic System				
Bone marrow	(52)	(53)	(53)	(54)
Lymph node	(14)	(6)	(9)	(3)
Lymph node, bronchial	(49)	(50)	(53)	(52)
Lymph node, mandibular	(47)	(45)	(51)	(49)
Squamous cell carcinoma, metastatic	1 (2%)			
Lymph node, mesenteric	(51)	(53)	(53)	(54)
Lymph node, mediastinal	(48)	(46)	(48)	(50)
Spleen	(53)	(53)	(53)	(54)
Hemangiosarcoma		1 (2%)		
Thymus	(48)	(49)	(47)	(47)
Thymoma NOS	1 (2%)			
Integumentary System				
Mammary gland	(53)	(53)	(53)	(54)
Adenoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Carcinoma			2 (4%)	1 (2%)
Carcinoma, multiple	1 (2%)		1 (2%)	
Fibroadenoma	11 (21%)	11 (21%)	13 (25%)	12 (22%)
Fibroadenoma, multiple	1 (2%)	3 (6%)	2 (4%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Integumentary System (continued)				
Skin	(4)	(3)	(3)	(5)
Basal cell adenoma	1 (25%)			
Fibroma				1 (20%)
Hemangioma		1 (33%)		
Keratoacanthoma	1 (25%)			
Papilloma				1 (20%)
Squamous cell carcinoma				1 (20%)
Squamous cell papilloma	2 (50%)			
Subcutaneous tissue, fibroma			1 (33%)	1 (20%)
Subcutaneous tissue, sarcoma			1 (33%)	
Musculoskeletal System				
Bone	(53)	(53)	(53)	(54)
Rib, osteosarcoma		1 (2%)		
Vertebra, schwannoma malignant, metastatic, peripheral nerve			1 (2%)	
Nervous System				
Brain	(53)	(53)	(53)	(54)
Carcinoma, metastatic	1 (2%)			1 (2%)
Cerebellum, carcinoma, metastatic		2 (4%)		1 (2%)
Cerebrum, carcinoma, metastatic		3 (6%)	1 (2%)	1 (2%)
Cerebrum, glioma NOS			1 (2%)	
Cerebrum, osteosarcoma, metastatic		1 (2%)		
Hypothalamus, carcinoma, metastatic		1 (2%)		
Peripheral nerve			(1)	
Schwannoma malignant			1 (100%)	
Respiratory System				
Lung	(53)	(53)	(53)	(54)
Alveolar/bronchiolar adenoma	1 (2%)		1 (2%)	3 (6%)
Alveolar/bronchiolar adenoma, multiple				1 (2%)
Alveolar/bronchiolar carcinoma			3 (6%)	
Alveolar/bronchiolar carcinoma, squamous differentiation			2 (4%)	1 (2%)
Carcinoma, metastatic, adrenal cortex	1 (2%)			
Osteosarcoma, metastatic		1 (2%)		
Special Senses System				
Zymbal's gland				(1)
Carcinoma				1 (100%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Urinary System				
Kidney	(53)	(53)	(53)	(54)
Liposarcoma			1 (2%)	
Mesenchymal tumor		1 (2%)		
Mixed tumor malignant				1 (2%)
Nephroblastoma			1 (2%)	
Transitional epithelium, carcinoma	1 (2%)			
Urinary bladder	(52)	(53)	(53)	(54)
Systemic Lesions				
Multiple organs[b]	(53)	(53)	(53)	(54)
Leukemia mononuclear	22 (42%)	19 (36%)	21 (40%)	18 (33%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
7-Month interim evaluation			1	
15-Month interim evaluation	1	4	2	3
2-Year study	52	49	51	50
Total primary neoplasms				
7-Month interim evaluation			1	
15-Month interim evaluation	2	4	2	3
2-Year study	91	80	93	97
Total animals with benign neoplasms				
7-Month interim evaluation			1	
15-Month interim evaluation	1	4	2	3
2-Year study	39	38	37	41
Total benign neoplasms				
7-Month interim evaluation			1	
15-Month interim evaluation	2	4	2	3
2-Year study	57	54	57	70
Total animals with malignant neoplasms				
2-Year study	32	25	30	25
Total malignant neoplasms				
2-Year study	33	25	35	27
Total animals with metastatic neoplasms				
2-Year study	3	5	3	2
Total metastatic neoplasms				
2-Year study	3	11	4	3
Total animals with uncertain neoplasms-benign or malignant				
2-Year study	1	1	1	
Total uncertain neoplasms				
2-Year study	1	1	1	

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³

Number of Days on Study	3 4 8	3 4 5	4 5 3	4 6 8	4 6 8	5 5 3	5 5 8	5 6 3	5 6 4	5 8 6	5 9 4	6 0 7	6 1 8	6 2 2	6 2 4	6 3 6	6 4 0	6 4 3	6 4 4	6 5 5	6 6 4	6 7 8	6 8 9	6 9 2	6 9 9
Carcass ID Number	0 9 6	1 0 8	0 8 5	1 1 9	1 2 2	0 9 1	0 8 6	0 9 4	0 7 5	0 9 8	0 7 0	1 1 1	0 7 3	1 2 4	1 1 4	0 1 4	1 2 6	1 0 9	0 7 7	1 1 0	0 7 9	0 6 7	1 3 0	1 2 5	1 0 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Odontoma																									
Cardiovascular System																									
Blood vessel																		+		+					+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									X
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pheochromocytoma benign							X																		
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X		X					X						X	X		X		X				
Pars distalis, carcinoma								X																	
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
General Body System																									
Tissue NOS		+		+						+									+					+	
Fibrosarcoma																			X						
Osteosarcoma		X																							
Squamous cell carcinoma										X														X	
Oral, squamous cell carcinoma																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma											X									X					

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³
(continued)

Number of Days on Study	7 1 3	7 1 3	7 1 4	7 1 4	7 1 5	7 2 7	7 2 7	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 7 2	1 0 0	1 0 7	1 1 7	1 2 1	1 0 4	1 2 9	0 4 7	0 8 0	0 8 2	0 9 2	1 0 5	1 0 6	0 8 3	1 1 3	1 2 7	0 7 1	0 8 1	0 8 8	0 8 9	0 9 0	0 9 9	1 0 3	1 1 2	1 1 6	1 1 8	1 2 0	1 2 8	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	52
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Tooth							+																					1
Odontoma							X																					1
Cardiovascular System																												
Blood vessel																												3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma																												1
Adrenal medulla	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign					X					X																		3
Bilateral, pheochromocytoma benign																			X									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma								X																				1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	52
Pars distalis, adenoma	X	X	X	X		X	X		X							X	X	X		X		X			X			20
Pars distalis, carcinoma																												1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell, adenoma															X													1
General Body System																												
Tissue NOS							+																					6
Fibrosarcoma																												1
Osteosarcoma																												1
Squamous cell carcinoma																												2
Oral, squamous cell carcinoma							X																					1
Genital System																												
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma																						X						1
Carcinoma																												2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³
(continued)

Number of Days on Study	3 4 8	3 5 4	4 0 3	4 6 8	4 6 8	5 5 3	5 5 8	5 6 3	5 6 4	5 8 6	5 9 4	6 0 7	6 1 8	6 2 2	6 2 4	6 3 6	6 4 0	6 4 3	6 4 4	6 5 5	6 6 4	6 7 8	6 8 9	6 9 2	6 9 9
Carcass ID Number	0 9 6	1 0 8	0 8 5	1 1 9	1 2 2	0 9 1	0 8 6	0 9 4	0 7 5	0 9 8	0 7 0	1 1 1	0 7 3	1 2 4	1 1 4	0 8 4	1 2 6	1 0 9	1 7 7	0 1 0	1 7 9	0 6 7	1 3 0	1 2 5	1 0 1
Genital System (continued)																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal													X	X										X	
Vagina																			+					+	
Polyp																			X						
Hematopoietic System																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+		+			+			+	+		+				+	+	+	
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																								X	
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	I	+	+	+
Thymoma NOS																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma, multiple																									
Fibroadenoma				X	X															X					
Fibroadenoma, multiple																								X	
Skin									+																
Basal cell adenoma																									
Keratoacanthoma																									
Squamous cell papilloma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic								X																	
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, adrenal cortex																									X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³
(continued)

Number of Days on Study	7 1 3	7 1 3	7 1 4	7 1 4	7 1 5	7 2 7	7 2 7	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 7 2	1 0 2	1 0 0 7	1 1 7	1 2 1	1 0 4	1 2 9	0 7 4	0 8 0	0 8 2	0 9 2	1 0 5	1 0 6	0 8 3	1 1 3	1 2 7	0 7 1	0 8 1	0 8 8	0 8 9	0 9 0	0 9 9	1 0 3	1 1 2	1 1 6	1 1 8	1 2 0	1 2 8	Total Tissues/ Tumors
Genital System (continued)																												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Granulosa-theca tumor benign															X													1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Polyp stromal										X		X									X	X		X	X			9
Vagina																												2
Polyp																												1
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node	+	+				+										+											+	14
Lymph node, bronchial	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	I	+	M	+	47
Squamous cell carcinoma, metastatic																												1
Lymph node, mesenteric	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mediastinal	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	48
Thymoma NOS																										X		1
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma									X																			1
Carcinoma, multiple								X																				1
Fibroadenoma			X				X	X						X		X	X					X		X				11
Fibroadenoma, multiple																												1
Skin													+											+	+			4
Basal cell adenoma																									X			1
Keratoacanthoma													X															1
Squamous cell papilloma																								X				2
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Skeletal muscle																										+		1
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma, metastatic																												1
Respiratory System																												
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Alveolar/bronchiolar adenoma										X																		1
Carcinoma, metastatic, adrenal cortex																												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³
(continued)

Number of Days on Study	3	3	4	4	4	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	4	5	0	6	6	5	5	6	6	8	9	0	1	2	2	3	4	4	4	5	6	7	8	9	9	
	8	4	3	8	8	3	8	3	4	6	4	7	8	2	4	6	0	3	4	5	4	8	9	2	9	
Carcass ID Number	0	1	0	1	1	0	0	0	0	0	0	1	0	1	1	0	1	1	0	1	0	0	1	1	1	
	9	0	8	1	2	9	8	9	7	9	7	1	7	2	1	8	2	0	7	1	7	6	3	2	0	
	6	8	5	9	2	1	6	4	5	8	0	1	3	4	4	4	6	9	7	0	9	7	0	5	1	
Special Senses System																										
Eye																		+			+		+			
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Transitional epithelium, carcinoma														X												
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear	X					X	X		X			X	X		X			X			X	X	X			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³
(continued)

Number of Days on Study	7 1 3	7 1 3	7 1 4	7 1 4	7 1 5	7 2 7	7 2 7	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 7 2	1 0 0	1 0 7	1 1 7	1 2 1	1 0 4	1 2 9	0 7 4	0 8 0	0 8 2	0 9 2	1 0 5	1 0 6	0 8 3	1 1 3	1 2 7	0 7 1	0 8 1	0 8 8	0 8 9	0 9 0	0 9 9	1 0 3	1 1 2	1 1 6	1 1 8	1 2 0	1 2 8	Total Tissues/ Tumors
Special Senses System																												
Eye																												3
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Transitional epithelium, carcinoma																												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear	X	X			X	X				X					X		X		X				X		X		X	22

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 0.62 mg/m³

Number of Days on Study	4 2 3	4 7 2	4 7 5	5 0 9	5 2 4	5 3 6	5 3 6	5 3 7	6 0 0	6 1 4	6 2 2	6 2 9	6 3 4	6 4 0	6 5 2	6 6 0	6 6 7	6 6 8	6 7 4	7 0 8	7 0 3	7 0 7	7 1 9	7 2 1	7 2 2
Carcass ID Number	2 3 1	2 3 3	2 3 5	1 9 6	2 3 8	1 9 8	2 0 7	2 5 9	2 5 4	1 9 7	2 0 3	2 1 0	2 4 0	2 1 5	2 4 8	2 2 6	2 5 3	2 5 2	2 2 3	1 9 9	2 3 0	2 1 6	2 3 7	2 3 5	2 2 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic																				X					
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																								+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic																				X					
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign				X									X						X					X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Osteosarcoma, metastatic																				X					
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X		X	X			X	X					X		X	X
Pars distalis, carcinoma				X			X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X												
General Body System																									
Tissue NOS													+												
Fibrous histiocytoma													X												
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X														X			
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Vagina				+																					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 0.62 mg/m³
(continued)

Number of Days on Study	7 2 5	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 2 2	2 2 9	2 0 6	2 0 8	2 3 9	2 4 1	2 4 7	2 4 9	2 5 6	2 5 5	2 0 2	2 1 7	2 1 8	2 2 1	2 2 4	2 3 2	2 5 7	2 5 8	2 0 0	2 0 4	2 1 1	2 4 5	2 5 0	2 5 1	2 0 9	2 1 3	2 1 4	2 1 9	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hepatocellular adenoma																											X		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Osteosarcoma, metastatic																													1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Cardiovascular System																													
Blood vessel																													1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Osteosarcoma, metastatic																													1
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal medulla	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pheochromocytoma benign				X															X	X									7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma																													1
Osteosarcoma, metastatic																													1
Parathyroid gland	+	+	+	+	I	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pars distalis, adenoma				X	X	X	X	X						X			X			X	X		X	X	X	X			21
Pars distalis, carcinoma		X																											3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell, adenoma																													1
General Body System																													
Tissue NOS																													1
Fibrous histiocytoma																													1
Genital System																													
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma														X								X							4
Bilateral, adenoma			X																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Polyp stromal		X							X																				2
Vagina																													1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 0.62 mg/m³
(continued)

Number of Days on Study	4 2 3	4 7 2	4 7 5	5 0 9	5 2 4	5 3 6	5 3 6	5 3 7	6 0 0	6 1 4	6 2 2	6 2 9	6 3 4	6 4 0	6 5 2	6 6 0	6 6 7	6 6 8	6 7 4	6 7 8	7 0 3	7 0 7	7 1 9	7 2 1	7 2 2
Carcass ID Number	2 3 1	2 3 3	2 2 5	1 9 6	2 3 8	1 9 8	2 0 7	2 5 9	2 5 4	1 9 7	2 0 3	2 1 0	2 4 0	2 1 5	2 4 8	2 2 6	2 5 3	2 5 2	2 2 3	1 9 9	2 3 0	2 1 6	2 3 7	2 3 5	2 2 8
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+	+					+				+					+			+		
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma			X											X						X		X		X	
Fibroadenoma, multiple									X																
Skin																						+	+	+	
Hemangioma																							X		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rib, osteosarcoma																					X				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebellum, carcinoma, metastatic				X			X																		
Cerebrum, carcinoma, metastatic				X			X																		
Cerebrum, osteosarcoma, metastatic																					X				
Hypothalamus, carcinoma, metastatic																									
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic																					X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+				+																				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesenchymal tumor																						X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X				X	X			X		X				X		X	X	X	X			X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 0.62 mg/m³
(continued)

Number of Days on Study	7 2 5	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 2 2 9	2 2 9 6	2 0 6 8	2 0 8 9	2 3 9 1	2 4 1 7	2 4 7 9	2 4 9 6	2 5 0 5	2 0 1 2	2 1 1 7	2 1 1 8	2 1 2 1	2 2 1 4	2 3 2 2	2 5 2 7	2 5 3 8	2 5 5 0	2 6 0 0	2 6 0 4	2 6 1 1	2 6 1 5	2 6 4 5	2 6 5 0	2 6 5 1	2 7 0 9	2 7 1 3	2 7 1 4	2 7 1 9	Total Tissues/ Tumors
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node																												6
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+	+	+	M	+	50
Lymph node, mandibular	+	+	+	+	M	+	M	+	I	+	+	+	+	+	I	+	+	+	+	+	M	M	+	+	+	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mediastinal	M	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hemangiosarcoma																												1
Thymus	+	+	I	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	53
Adenoma																						X						1
Fibroadenoma	X					X	X																	X	X		X	11
Fibroadenoma, multiple														X									X					3
Skin																												3
Hemangioma																												1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Rib, osteosarcoma																												1
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Cerebellum, carcinoma, metastatic																												2
Cerebrum, carcinoma, metastatic		X																										3
Cerebrum, osteosarcoma, metastatic																												1
Hypothalamus, carcinoma, metastatic						X																						1
Respiratory System																												
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Osteosarcoma, metastatic																												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																												
Eye																												2
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Mesenchymal tumor																												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear									X	X		X	X		X							X		X			X	19

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³

Number of Days on Study	3 4 4 4 4 4 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 4 3 6 7 7 9 0 1 3 6 9 1 1 1 2 3 3 4 4 4 4 5 8 8 9 6 6 6 1 6 4 3 4 6 5 4 1 4 8 7 4 8 0 3 3 7 5 6 9 0
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 6 8 8 7 5 4 7 8 5 8 7 8 6 5 8 6 5 5 3 5 7 6 8 5 3 1 9 2 4 3 4 5 6 4 1 7 4 5 2 7 8 1 5 6 6 8 7 0 8 5
Alimentary System	
Esophagus	+ +
Sarcoma, metastatic	X
Intestine large, colon	+ +
Intestine large, rectum	+ + + + + + + + + + + + + + + + I + + + + + + +
Intestine large, cecum	+ +
Intestine small, duodenum	+ +
Intestine small, jejunum	+ +
Intestine small, ileum	+ +
Liver	+ +
Sarcoma, metastatic	X
Pancreas	+ +
Salivary glands	+ + + + + + M + + + + + + + + + + + + + + + + +
Stomach, forestomach	+ +
Stomach, glandular	+ +
Cardiovascular System	
Blood vessel	+
Heart	+ +
Endocrine System	
Adrenal cortex	+ +
Adrenal medulla	+ +
Pheochromocytoma benign	X X
Bilateral, pheochromocytoma benign	
Islets, pancreatic	+ +
Adenoma	
Parathyroid gland	+ + + + + + + M M + + + + + M + + + + + + + + +
Pituitary gland	+ +
Pars distalis, adenoma	X X X X X X X
Pars distalis, carcinoma	
Thyroid gland	+ +
C-cell, adenoma	
General Body System	
Tissue NOS	+ +
Lipoma	X
Liposarcoma	X
Genital System	
Clitoral gland	+ + + + + + + M + + + + + + + + + + + + + + + +
Adenoma	
Bilateral, adenoma	
Ovary	+ +
Uterus	+ +
Polyp stromal	X
Vagina	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	6 9 0	6 9 0	7 1 3	7 1 3	7 2 2	7 2 7	7 2 7	7 2 7	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 4 3	3 4 5	3 4 6	3 7 9	3 2 7	3 4 9	3 7 6	3 8 3	3 3 0	3 6 3	3 7 1	3 7 2	3 3 7	3 4 1	3 5 9	3 6 0	3 6 2	3 6 9	3 2 6	3 2 8	3 3 1	3 3 4	3 4 7	3 4 8	3 5 0	3 3 9	3 6 6	3 7 3	Total Tissues\ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Sarcoma, metastatic																													1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Sarcoma, metastatic																													1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Cardiovascular System																													
Blood vessel	+																												2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma benign			X				X											X										5
Bilateral, pheochromocytoma benign																	X												1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma																								X					1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	52
Pars distalis, adenoma				X	X	X	X	X	X	X						X				X		X			X		X		19
Pars distalis, carcinoma			X																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
C-cell, adenoma												X								X				X					3
General Body System																													
Tissue NOS													+																3
Lipoma													X																2
Liposarcoma																													1
Genital System																													
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																											X		1
Bilateral, adenoma																							X						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Uterus	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Polyp stromal		X			X	X	X										X												6
Vagina					+																								1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	3 4 4 4 4 4 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 4 3 6 7 7 9 0 1 3 6 9 1 1 1 2 3 3 4 4 4 4 5 8 8 9 6 6 6 1 6 4 3 4 6 5 4 1 4 8 7 4 8 0 3 3 7 5 6 9 0
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 6 8 8 7 5 4 7 8 5 8 7 8 6 5 8 6 5 5 3 5 7 6 8 5 3 1 9 2 4 3 4 5 6 4 1 7 4 5 2 7 8 1 5 6 6 8 7 0 8 5
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ +
Lymph node, bronchial	+ +
Lymph node, mandibular	+ + + + + + M + + + + + + + + + + + + + + + + +
Lymph node, mesenteric	+ +
Lymph node, mediastinal	+ + + + + + + M + + + + + + + + M M + + + + + +
Spleen	+ +
Thymus	+ + + + + + + + + + + + + M + + + + + + + + + +
Integumentary System	
Mammary gland	+ +
Adenoma	X
Carcinoma	X
Carcinoma, multiple	
Fibroadenoma	X X X X X
Fibroadenoma, multiple	
Skin	+ + +
Subcutaneous tissue, fibroma	X
Subcutaneous tissue, sarcoma	X
Musculoskeletal System	
Bone	+ +
Vertebra, schwannoma malignant, metastatic, peripheral nerve	X
Nervous System	
Brain	+ +
Cerebrum, carcinoma, metastatic	
Cerebrum, glioma NOS	X
Peripheral nerve	+
Schwannoma malignant	X
Respiratory System	
Larynx	+ +
Lung	+ +
Alveolar/bronchiolar adenoma	X
Alveolar/bronchiolar carcinoma	X
Alveolar/bronchiolar carcinoma, squamous differentiation	
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	+ + + + +

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	6 9 0	6 9 0	7 1 3	7 1 3	7 2 2	7 2 7	7 2 7	7 2 7	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 4 3	3 4 5	3 4 6	3 7 9	3 2 7	3 4 9	3 7 6	3 8 3	3 3 0	3 6 3	3 7 1	3 7 2	3 3 7	3 4 1	3 5 9	3 6 0	3 6 2	3 6 9	3 2 6	3 2 8	3 3 1	3 3 4	3 4 7	3 4 8	3 5 0	3 3 9	3 6 6	3 7 3	Total Tissues/ Tumors
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node	+				+							+											+						9
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	M	+	+	+	M	+	47
Integumentary System																													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma																													1
Carcinoma										X																			2
Carcinoma, multiple																						X							1
Fibroadenoma					X					X				X			X			X	X	X					X	X	13
Fibroadenoma, multiple		X		X																									2
Skin																													3
Subcutaneous tissue, fibroma																													1
Subcutaneous tissue, sarcoma																													1
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Vertebra, schwannoma malignant, metastatic, peripheral nerve																													1
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Cerebrum, carcinoma, metastatic				X																									1
Cerebrum, glioma NOS																													1
Peripheral nerve																													1
Schwannoma malignant																													1
Respiratory System																													
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Alveolar/bronchiolar adenoma																													1
Alveolar/bronchiolar carcinoma															X			X											3
Alveolar/bronchiolar carcinoma, squamous differentiation											X											X							2
Nose	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																													
Eye																									+				5

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	3 4 4 4 4 4 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 4 3 6 7 7 9 0 1 3 6 9 1 1 1 2 3 3 4 4 4 4 5 8 8 9 6 6 6 1 6 4 3 4 6 5 4 1 4 8 7 4 8 0 3 3 7 5 6 9 0
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 6 8 8 7 5 4 7 8 5 8 7 8 6 5 8 6 5 5 3 5 7 6 8 5 3 1 9 2 4 3 4 5 6 4 1 7 4 5 2 7 8 1 5 6 6 8 7 0 8 5
Urinary System	
Kidney	+ +
Liposarcoma	X
Nephroblastoma	X
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X X X X X X X X X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	6 9 0	6 9 0	7 1 3	7 1 3	7 2 2	7 2 7	7 2 7	7 2 7	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 4 3	3 4 5	3 4 6	3 7 9	3 2 7	3 4 9	3 7 6	3 8 3	3 3 0	3 6 3	3 7 1	3 7 2	3 3 7	3 4 1	3 5 9	3 6 0	3 6 2	3 6 9	3 2 6	3 2 8	3 3 1	3 3 4	3 4 7	3 4 8	3 5 0	3 3 9	3 6 6	3 7 3	Total Tissues/ Tumors
Urinary System																													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Liposarcoma																													1
Nephroblastoma																													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Systemic Lesions																													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear	X				X		X					X					X		X			X				X		X	21

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³

Number of Days on Study	0 9 0	4 6 6	4 6 7	4 9 4	4 9 6	5 1 9	5 3 8	5 3 9	5 5 0	5 5 9	5 7 0	5 7 0	5 7 7	5 7 0	6 0 7	6 0 9	6 0 8	6 1 3	6 3 6	6 3 5	6 5 3	6 6 4	6 7 1	7 0 4	7 0 6
Carcass ID Number	4 6 1	4 9 9	4 6 6	5 1 7	4 8 3	5 1 1	5 0 5	4 9 0	4 9 4	4 9 2	4 6 7	4 8 2	4 9 5	4 9 1	5 1 8	4 1 2	4 7 1	4 8 1	5 0 9	4 9 7	4 6 4	4 9 8	4 7 6	4 5 8	5 1 9	4 8 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery																									
Lipoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parotid gland, adenoma																									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pheochromocytoma benign						X													X			X		X	
Bilateral, pheochromocytoma benign																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X					X	X		X			X					X	X
Pars distalis, carcinoma									X													X			
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
General Body System																									
Tissue NOS																		+			+				
Fibroma																		X							
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Carcinoma															X										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal		X																							
Schwannoma malignant																					X				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	7 1 8	7 1 9	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	4 6 8	4 7 4	5 0 7	4 6 2	4 6 5	4 7 3	4 9 3	5 0 0	5 0 2	5 1 4	5 1 5	4 7 7	4 7 8	4 8 0	4 8 8	5 1 6	5 2 0	4 6 9	4 7 0	4 8 4	4 8 9	5 0 3	5 1 2	5 1 3	5 5 7	4 6 0	4 7 1	4 7 5	4 7 9	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Lipoma					X																								1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Hepatocellular adenoma												X																	1
Mesentery																				+									1
Lipoma																				X									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	53
Parotid gland, adenoma																				X									1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Tooth		+																											1
Cardiovascular System																													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma benign					X			X			X			X						X			X			X	X		X		13
Bilateral, pheochromocytoma benign												X	X			X								X							5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Pars distalis, adenoma	X		X	X				X	X					X	X		X						X	X	X		X	X		20
Pars distalis, carcinoma																															2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
C-cell, adenoma																											X		X		2
General Body System																															
Tissue NOS																		+													3
Fibroma																															1
Genital System																															
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+		50
Carcinoma																															1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		54
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		54
Polyp stromal				X	X						X										X										5
Schwannoma malignant																															1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	0 9 0	4 6 6	4 6 7	4 9 4	4 9 6	5 1 9	5 3 8	5 3 9	5 5 0	5 5 9	5 7 0	5 7 0	5 7 7	5 7 0	6 0 0	6 0 7	6 1 9	6 3 8	6 3 3	6 5 6	6 6 5	6 6 3	6 6 4	7 7 1	7 0 4	7 0 6
Carcass ID Number	4 6 1	4 9 1	4 6 9	5 1 7	4 8 3	5 1 1	5 0 5	4 9 0	4 9 4	4 9 2	4 6 7	4 8 2	4 9 5	4 9 1	5 1 8	4 2 2	4 7 1	5 8 2	4 0 1	4 9 9	4 6 7	4 9 4	4 7 6	5 5 8	5 1 9	4 8 6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node												+											+			
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	+	+	M	+	+	+	I	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Carcinoma							X																			
Fibroadenoma			X						X								X								X	
Skin																								+		
Fibroma																								X		
Papilloma																										
Squamous cell carcinoma																										
Subcutaneous tissue, fibroma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic									X																	
Cerebellum, carcinoma, metastatic																							X			
Cerebrum, carcinoma, metastatic																							X			
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar adenoma, multiple																										
Alveolar/bronchiolar carcinoma, squamous differentiation																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye					+													+								
Zymbal's gland										+																
Carcinoma										X																

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	7 1 8	7 1 9	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	4 6 8	4 7 4	5 0 7	4 6 2	4 6 5	4 7 3	4 9 3	5 0 0	5 0 2	5 1 4	5 1 5	4 7 7	4 7 8	4 8 0	4 8 8	5 1 6	5 2 0	4 6 9	4 7 0	4 8 4	4 8 9	5 0 3	5 1 2	5 1 3	5 5 7	4 6 0	4 7 1	4 7 5	4 7 9	Total Tissues/ Tumors
Hematopoietic System																														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Lymph node																+														3
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	M	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Thymus	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	47
Integumentary System																														
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Adenoma						X																								1
Carcinoma																														1
Fibroadenoma							X				X		X			X	X							X	X				X	12
Skin	+													+				+										+		5
Fibroma																														1
Papilloma														X																1
Squamous cell carcinoma	X																													1
Subcutaneous tissue, fibroma																												X		1
Musculoskeletal System																														
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Nervous System																														
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Carcinoma, metastatic																														1
Cerebellum, carcinoma, metastatic																														1
Cerebrum, carcinoma, metastatic																														1
Respiratory System																														
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Alveolar/bronchiolar adenoma					X		X																			X				3
Alveolar/bronchiolar adenoma, multiple													X																	1
Alveolar/bronchiolar carcinoma, squamous differentiation											X																			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Special Senses System																														
Eye																							+							3
Zymbal's gland																														1
Carcinoma																														1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	0	4	4	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7
	9	6	6	9	9	1	3	3	5	5	7	7	7	0	0	0	1	3	3	5	6	6	7	0	0
	0	6	7	4	6	9	8	9	0	9	0	0	7	0	7	9	8	3	6	5	3	4	1	4	6
Carcass ID Number	4	4	4	5	4	5	5	4	4	4	4	4	4	4	5	4	4	5	4	4	4	4	5	4	
	6	9	6	1	8	1	0	9	9	9	6	8	9	9	1	7	8	0	9	6	9	7	5	1	8
	1	9	6	7	3	1	5	0	4	2	7	2	5	1	8	2	1	9	7	4	8	6	8	9	6
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mixed tumor malignant							X																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X			X			X	X						X	X	X		X		X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	7 1 8	7 1 9	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	4 6 8	4 7 4	5 0 7	4 6 2	4 6 5	4 7 3	4 9 3	5 0 0	5 0 2	5 1 4	5 1 5	4 7 7	4 7 8	4 8 0	4 8 8	5 1 6	5 2 0	4 6 9	4 7 0	4 8 4	4 8 9	5 0 3	5 1 2	5 1 3	4 5 7	4 6 0	4 7 1	4 7 5	4 7 9	Total Tissues/ Tumors
Urinary System																														
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Mixed tumor malignant																														1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Systemic Lesions																														
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Leukemia mononuclear		X	X									X	X			X	X						X						X	18

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Oxide

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	4/51 (8%)	7/52 (13%)	6/53 (11%)	18/53 (34%)
Adjusted rate[b]	15.1%	21.1%	22.0%	56.5%
Terminal rate[c]	2/21 (10%)	3/25 (12%)	2/20 (10%)	13/26 (50%)
First incidence (days)	558	524	611	519
Life table test[d]	P<0.001	P=0.350	P=0.353	P=0.003
Logistic regression test[d]	P<0.001	P=0.288	P=0.385	P=0.001
Cochran-Armitage test[d]	P<0.001			
Fisher exact test[d]		P=0.274	P=0.395	P<0.001
Clitoral Gland: Adenoma				
Overall rate	1/53 (2%)	5/53 (9%)	2/51 (4%)	0/50 (0%)
Adjusted rate	4.8%	16.2%	10.0%	0.0%
Terminal rate	1/21 (5%)	3/26 (12%)	2/20 (10%)	0/24 (0%)
First incidence (days)	729 (T)	537	729 (T)	—[e]
Life table test	P=0.151N	P=0.145	P=0.483	P=0.473N
Logistic regression test	P=0.183N	P=0.114	P=0.483	P=0.473N
Cochran-Armitage test	P=0.176N			
Fisher exact test		P=0.103	P=0.485	P=0.515N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	3/53 (6%)	5/53 (9%)	2/51 (4%)	1/50 (2%)
Adjusted rate	9.8%	16.2%	10.0%	2.5%
Terminal rate	1/21 (5%)	3/26 (12%)	2/20 (10%)	0/24 (0%)
First incidence (days)	594	537	729 (T)	607
Life table test	P=0.136N	P=0.436	P=0.519N	P=0.305N
Logistic regression test	P=0.158N	P=0.367	P=0.521N	P=0.324N
Cochran-Armitage test	P=0.154N			
Fisher exact test		P=0.358	P=0.518N	P=0.331N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/53 (2%)	0/53 (0%)	1/53 (2%)	4/54 (7%)
Adjusted rate	4.8%	0.0%	3.1%	15.4%
Terminal rate	1/21 (5%)	0/26 (0%)	0/20 (0%)	4/26 (15%)
First incidence (days)	729 (T)	—	655	729 (T)
Life table test	P=0.044	P=0.457N	P=0.748	P=0.245
Logistic regression test	P=0.032	P=0.457N	P=0.759	P=0.245
Cochran-Armitage test	P=0.035			
Fisher exact test		P=0.500N	P=0.752N	P=0.187
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	0/53 (0%)	0/53 (0%)	5/53 (9%)	1/54 (2%)
Adjusted rate	0.0%	0.0%	22.3%	3.8%
Terminal rate	0/21 (0%)	0/26 (0%)	4/20 (20%)	1/26 (4%)
First incidence (days)	—	—	643	729 (T)
Life table test	P=0.302	—	P=0.029	P=0.543
Logistic regression test	P=0.262	—	P=0.029	P=0.543
Cochran-Armitage test	P=0.272			
Fisher exact test		—	P=0.028	P=0.505

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	1/53 (2%)	0/53 (0%)	6/53 (11%)	5/54 (9%)
Adjusted rate	4.8%	0.0%	24.7%	19.2%
Terminal rate	1/21 (5%)	0/26 (0%)	4/20 (20%)	5/26 (19%)
First incidence (days)	729 (T)	—	643	729 (T)
Life table test	P=0.035	P=0.457N	P=0.051	P=0.152
Logistic regression test	P=0.022	P=0.457N	P=0.053	P=0.152
Cochran-Armitage test	P=0.026			
Fisher exact test		P=0.500N	P=0.056	P=0.107
Mammary Gland: Fibroadenoma				
Overall rate	12/53 (23%)	14/53 (26%)	15/53 (28%)	12/54 (22%)
Adjusted rate	40.9%	40.1%	52.5%	37.4%
Terminal rate	6/21 (29%)	7/26 (27%)	8/20 (40%)	8/26 (31%)
First incidence (days)	468	475	614	467
Life table test	P=0.414N	P=0.574N	P=0.297	P=0.439N
Logistic regression test	P=0.510N	P=0.445	P=0.305	P=0.578N
Cochran-Armitage test	P=0.481N			
Fisher exact test		P=0.411	P=0.328	P=0.571N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	13/53 (25%)	15/53 (28%)	16/53 (30%)	13/54 (24%)
Adjusted rate	44.8%	43.3%	53.6%	40.9%
Terminal rate	7/21 (33%)	8/26 (31%)	8/20 (40%)	9/26 (35%)
First incidence (days)	468	475	611	467
Life table test	P=0.409N	P=0.555N	P=0.301	P=0.422N
Logistic regression test	P=0.511N	P=0.455	P=0.309	P=0.575N
Cochran-Armitage test	P=0.480N			
Fisher exact test		P=0.413	P=0.332	P=0.567N
Mammary Gland: Carcinoma				
Overall rate	1/53 (2%)	0/53 (0%)	3/53 (6%)	1/54 (2%)
Adjusted rate	4.8%	0.0%	12.6%	2.1%
Terminal rate	1/21 (5%)	0/26 (0%)	2/20 (10%)	0/26 (0%)
First incidence (days)	729 (T)	—	643	538
Life table test	P=0.511	P=0.457N	P=0.290	P=0.737N
Logistic regression test	P=0.488	P=0.457N	P=0.294	P=0.756N
Cochran-Armitage test	P=0.492			
Fisher exact test		P=0.500N	P=0.309	P=0.748N
Mammary Gland: Adenoma or Carcinoma				
Overall rate	2/53 (4%)	1/53 (2%)	4/53 (8%)	2/54 (4%)
Adjusted rate	9.5%	3.8%	14.7%	5.8%
Terminal rate	2/21 (10%)	1/26 (4%)	2/20 (10%)	1/26 (4%)
First incidence (days)	729 (T)	729 (T)	611	538
Life table test	P=0.525	P=0.425N	P=0.323	P=0.636N
Logistic regression test	P=0.488	P=0.425N	P=0.327	P=0.690N
Cochran-Armitage test	P=0.498			
Fisher exact test		P=0.500N	P=0.339	P=0.684N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	13/53 (25%)	15/53 (28%)	17/53 (32%)	14/54 (26%)
Adjusted rate	44.8%	43.3%	54.9%	42.1%
Terminal rate	7/21 (33%)	8/26 (31%)	8/20 (40%)	9/26 (35%)
First incidence (days)	468	475	611	467
Life table test	P=0.506N	P=0.555N	P=0.237	P=0.509N
Logistic regression test	P=0.476	P=0.455	P=0.238	P=0.516
Cochran-Armitage test	P=0.505			
Fisher exact test		P=0.413	P=0.259	P=0.522
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	20/52 (38%)	21/52 (40%)	19/52 (37%)	20/54 (37%)
Adjusted rate	57.4%	60.1%	60.3%	55.7%
Terminal rate	7/20 (35%)	13/26 (50%)	8/19 (42%)	11/26 (42%)
First incidence (days)	403	614	536	539
Life table test	P=0.378N	P=0.375N	P=0.548N	P=0.381N
Logistic regression test	P=0.479N	P=0.575N	P=0.519N	P=0.524N
Cochran-Armitage test	P=0.437N			
Fisher exact test		P=0.500	P=0.500N	P=0.519N
Pituitary Gland (Pars Distalis): Carcinoma				
Overall rate	1/52 (2%)	3/52 (6%)	1/52 (2%)	2/54 (4%)
Adjusted rate	2.2%	7.5%	3.8%	5.1%
Terminal rate	0/20 (0%)	0/26 (0%)	0/19 (0%)	0/26 (0%)
First incidence (days)	563	509	713	550
Life table test	P=0.527	P=0.326	P=0.747	P=0.490
Logistic regression test	P=0.579	P=0.221	P=0.762N	P=0.531
Cochran-Armitage test	P=0.544			
Fisher exact test		P=0.309	P=0.752N	P=0.514
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	21/52 (40%)	24/52 (46%)	20/52 (38%)	22/54 (41%)
Adjusted rate	58.3%	63.1%	61.8%	58.0%
Terminal rate	7/20 (35%)	13/26 (50%)	8/19 (42%)	11/26 (42%)
First incidence (days)	403	509	536	539
Life table test	P=0.408N	P=0.506N	P=0.550N	P=0.454N
Logistic regression test	P=0.497N	P=0.397	P=0.518N	P=0.560
Cochran-Armitage test	P=0.461N			
Fisher exact test		P=0.346	P=0.500N	P=0.564
Skin: Papilloma, Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, or Squamous Cell Carcinoma				
Overall rate	4/53 (8%)	0/53 (0%)	0/53 (0%)	2/54 (4%)
Adjusted rate	16.2%	0.0%	0.0%	7.2%
Terminal rate	3/21 (14%)	0/26 (0%)	0/20 (0%)	1/26 (4%)
First incidence (days)	564	—	—	718
Life table test	P=0.324N	P=0.045N	P=0.069N	P=0.261N
Logistic regression test	P=0.363N	P=0.058N	P=0.065N	P=0.329N
Cochran-Armitage test	P=0.354N			
Fisher exact test		P=0.059N	P=0.059N	P=0.330N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Thyroid Gland (C-cell): Adenoma				
Overall rate	1/52 (2%)	1/52 (2%)	3/53 (6%)	2/53 (4%)
Adjusted rate	4.8%	2.4%	15.0%	7.7%
Terminal rate	1/21 (5%)	0/26 (0%)	3/20 (15%)	2/26 (8%)
First incidence (days)	729 (T)	634	729 (T)	729 (T)
Life table test	P=0.378	P=0.728N	P=0.284	P=0.575
Logistic regression test	P=0.333	P=0.759N	P=0.284	P=0.575
Cochran-Armitage test	P=0.343			
Fisher exact test		P=0.752N	P=0.316	P=0.507
Tissue NOS: Squamous Cell Carcinoma				
Overall rate	3/53 (6%)	0/53 (0%)	0/53 (0%)	0/54 (0%)
Adjusted rate	9.6%	0.0%	0.0%	0.0%
Terminal rate	0/21 (0%)	0/26 (0%)	0/20 (0%)	0/26 (0%)
First incidence (days)	586	—	—	—
Life table test	P=0.055N	P=0.110N	P=0.134N	P=0.119N
Logistic regression test	P=0.052N	P=0.119N	P=0.122N	P=0.118N
Cochran-Armitage test	P=0.052N			
Fisher exact test		P=0.121N	P=0.121N	P=0.118N
Uterus: Stromal Polyp				
Overall rate	9/53 (17%)	2/53 (4%)	6/53 (11%)	5/54 (9%)
Adjusted rate	34.3%	7.3%	21.6%	17.0%
Terminal rate	6/21 (29%)	1/26 (4%)	1/20 (5%)	4/26 (15%)
First incidence (days)	618	725	594	466
Life table test	P=0.259N	P=0.014N	P=0.321N	P=0.122N
Logistic regression test	P=0.309N	P=0.019N	P=0.303N	P=0.186N
Cochran-Armitage test	P=0.293N			
Fisher exact test		P=0.026N	P=0.289N	P=0.185N
All Organs: Mononuclear Cell Leukemia				
Overall rate:	22/53 (42%)	19/53 (36%)	21/53 (40%)	18/54 (33%)
Adjusted rate:	57.2%	47.7%	55.6%	44.7%
Terminal rate:	7/21 (33%)	8/26 (31%)	6/20 (30%)	6/26 (23%)
First incidence (days)	348	423	494	466
Life table test	P=0.269N	P=0.222N	P=0.545N	P=0.221N
Logistic regression test	P=0.254N	P=0.359N	P=0.502N	P=0.250N
Cochran-Armitage test	P=0.257N			
Fisher exact test		P=0.345N	P=0.500N	P=0.250N
All Organs: Benign Neoplasms				
Overall rate	40/53 (75%)	39/53 (74%)	37/53 (70%)	41/54 (76%)
Adjusted rate	90.6%	86.3%	92.2%	95.2%
Terminal rate	17/21 (81%)	20/26 (77%)	17/20 (85%)	24/26 (92%)
First incidence (days)	403	475	466	466
Life table test	P=0.433N	P=0.194N	P=0.469N	P=0.340N
Logistic regression test	P=0.444	P=0.411N	P=0.349N	P=0.553
Cochran-Armitage test	P=0.512			
Fisher exact test		P=0.500N	P=0.332N	P=0.567

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
All Organs: Malignant Neoplasms				
Overall rate	32/53 (60%)	26/53 (49%)	30/53 (57%)	25/54 (46%)
Adjusted rate	69.3%	57.9%	72.2%	55.0%
Terminal rate	8/21 (38%)	9/26 (35%)	10/20 (50%)	7/26 (27%)
First incidence (days)	348	423	436	466
Life table test	P=0.193N	P=0.121N	P=0.502N	P=0.136N
Logistic regression test	P=0.110N	P=0.177N	P=0.416N	P=0.091N
Cochran-Armitage test	P=0.134N			
Fisher exact test		P=0.165N	P=0.422N	P=0.103N
All Organs: Benign or Malignant Neoplasms				
Overall rate	52/53 (98%)	49/53 (92%)	51/53 (96%)	50/54 (93%)
Adjusted rate	98.1%	94.2%	100.0%	96.2%
Terminal rate	20/21 (95%)	23/26 (88%)	20/20 (100%)	24/26 (92%)
First incidence (days)	348	423	436	466
Life table test	P=0.318N	P=0.123N	P=0.512	P=0.217N
Logistic regression test	P=0.277N	P=0.185N	P=0.497N	P=0.207N
Cochran-Armitage test	P=0.226N			
Fisher exact test		P=0.181N	P=0.500N	P=0.187N

(T)Terminal sacrifice

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, lung, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.

[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by **N**.

[e] Not applicable; no neoplasms in animal group

TABLE B4a
Historical Incidence of Lung Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls			
	Alveolar/bronchiolar Adenoma	Alveolar/bronchiolar Carcinoma	Squamous Cell Carcinoma	Alveolar/bronchiolar Adenoma or Carcinoma or Squamous Cell Carcinoma
Historical Incidence at Lovelace Inhalation Toxicology Research Institute				
Nickel Oxide	1/53	0/53	0/53	1/53
Nickel Subsulfide	2/53	0/53	0/53	2/53
Nickel Sulfate Hexahydrate	0/52	0/52	0/52	0/52
Talc[b]	1/50	0/50	0/50	1/50
Overall Historical Incidence in Inhalation Studies				
Total	7/700 (1.1%)	0/700 (0%)	0/700 (0%)	8/700 (1.1%)
Standard deviation	1.5%			1.5%
Range	0%-4%			0%-4%
Overall Historical Incidence in Feed Studies				
Total	20/1,201 (1.7%)	5/1,201 (0.4%)	0/1,201 (0%)	25/1,201 (2.1%)
Standard deviation	2.2%	0.8%		2.2%
Range	0%-10%	0%-2%		0%-10%

[a] Data as of 17 June 1994
[b] Results of lifetime study; others are 2-year studies

TABLE B4b
Historical Incidence of Pheochromocytomas of the Adrenal Medulla in Untreated Female F344/N Rats[a]

Study	Incidence in Controls				
	Benign	Complex	Malignant	NOS	Benign, Complex, Malignant, or NOS
Historical Incidence at Lovelace Inhalation Toxicology Research Institute[b]					
Nickel Oxide	4/51	0/51	0/51	0/51	4/51
Nickel Subsulfide	2/53	0/53	1/53	0/53	3/53
Nickel Sulfate Hexahydrate	2/51	0/51	0/51	0/51	2/51
Overall Historical Incidence in Inhalation Studies					
Total	35/608 (5.8%)	2/608 (0.3%)	1/608 (0.2%)	1/608 (0.2%)	39/608 (6.4%)
Standard deviation	4.9%	1.1%	0.6%	0.6%	4.4%
Range	0%-14%	0%-4%	0%-2%	0%-2%	2%-14%
Overall Historical Incidence in Feed Studies					
Total	49/1,175 (4.2%)	2/1,175 (0.2%)	6/1,175 (0.5%)	6/1,175 (0.5%)	62/1,175 (5.3%)
Standard deviation	2.5%	0.6%	0.9%	2.5%	2.8%
Range	0%-8%	0%-2%	0%-2%	0%-12%	2%-12%

[a] Data as of 17 June 1994
[b] Talc excluded because it was not a 2-year study.

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Disposition Summary				
Animals initially in study	65	65	65	65
7-Month interim evaluation	7	7	7	6
15-Month interim evaluation	5	5	5	5
Early deaths				
Moribund	27	24	27	25
Natural deaths	5	3	6	3
Survivors				
Terminal sacrifice	21	26	20	26
Animals examined microscopically	65	65	65	65
7-Month Interim Evaluation				
Alimentary System				
Liver	(1)			
Hepatodiaphragmatic nodule	1 (100%)			
Endocrine System				
Pituitary gland		(2)	(3)	(1)
Pars distalis, hyperplasia, diffuse		2 (100%)	3 (100%)	1 (100%)
Genital System				
Ovary			(2)	
Cyst			2 (100%)	
Hematopoietic System				
Lymph node, bronchial	(6)	(7)	(7)	(6)
Hyperplasia, lymphoid			4 (57%)	3 (50%)
Pigmentation			7 (100%)	6 (100%)
Lymph node, mediastinal	(6)	(7)	(6)	(5)
Pigmentation			2 (33%)	3 (60%)
Respiratory System				
Lung	(7)	(7)	(7)	(6)
Inflammation, chronic	1 (14%)		7 (100%)	6 (100%)
Alveolar epithelium, pigmentation		1 (14%)		
Alveolus, pigmentation		5 (71%)	7 (100%)	6 (100%)
Special Senses System				
Eye			(1)	
Cornea, degeneration			1 (100%)	

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m^3	0.62 mg/m^3	1.25 mg/m^3	2.5 mg/m^3
7-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(7)	(7)	(7)	(6)
Cortex, infiltration cellular, lymphocyte			1 (14%)	1 (17%)
Urinary bladder				(1)
Edema, focal				1 (100%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
15-Month Interim Evaluation				
Endocrine System				
Adrenal medulla	(5)	(5)	(4)	(5)
Hyperplasia	1 (20%)		1 (25%)	
Pituitary gland	(5)	(5)	(5)	(5)
Pars distalis, hyperplasia			1 (20%)	
Pars distalis, hyperplasia, cystic	1 (20%)			
Genital System				
Ovary	(5)	(5)	(5)	(5)
Cyst	1 (20%)	2 (40%)	1 (20%)	
Hematopoietic System				
Lymph node				(1)
Hyperplasia, lymphoid				1 (100%)
Lymph node, bronchial	(5)	(5)	(5)	(5)
Hyperplasia, lymphoid			3 (60%)	3 (60%)
Pigmentation		4 (80%)	5 (100%)	5 (100%)
Lymph node, mediastinal	(5)	(5)	(4)	(4)
Hyperplasia, lymphoid				3 (75%)
Pigmentation		3 (60%)	4 (100%)	3 (75%)
Nervous System				
Brain	(5)	(5)	(5)	(5)
Ventricle, ectasia	1 (20%)			
Respiratory System				
Lung	(5)	(5)	(5)	(5)
Inflammation, chronic	3 (60%)	4 (80%)	5 (100%)	5 (100%)
Alveolus, pigmentation		5 (100%)	5 (100%)	5 (100%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(5)	(5)	(5)	(5)
Nephropathy	4 (80%)	4 (80%)	5 (100%)	2 (40%)
Urinary bladder	(5)	(5)	(5)	(5)
Calculus, microscopic observation only	1 (20%)			
Systems Examined With No Lesions Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Integumentary System				
Musculoskeletal System				
Special Senses System				
2-Year Study				
Alimentary System				
Intestine large, colon	(52)	(53)	(53)	(54)
Inflammation, chronic active	1 (2%)			
Mineralization			1 (2%)	
Parasite metazoan		2 (4%)	1 (2%)	
Intestine large, rectum	(52)	(53)	(52)	(54)
Parasite metazoan	2 (4%)		2 (4%)	5 (9%)
Intestine large, cecum	(52)	(53)	(53)	(54)
Parasite metazoan			1 (2%)	
Liver	(53)	(53)	(53)	(54)
Angiectasis		2 (4%)	1 (2%)	1 (2%)
Basophilic focus	26 (49%)	38 (72%)	27 (51%)	34 (63%)
Clear cell focus		1 (2%)		
Congestion	2 (4%)	1 (2%)	3 (6%)	
Cyst	1 (2%)			
Degeneration, cystic		1 (2%)	2 (4%)	1 (2%)
Eosinophilic focus	2 (4%)	3 (6%)	3 (6%)	2 (4%)
Fatty change	21 (40%)	18 (34%)	16 (30%)	15 (28%)
Fibrosis		1 (2%)		
Granuloma	1 (2%)			
Hemorrhage		1 (2%)		
Hepatodiaphragmatic nodule	7 (13%)	3 (6%)	9 (17%)	4 (7%)
Inflammation, chronic				1 (2%)
Mixed cell focus	1 (2%)			
Pigmentation, bile	1 (2%)	1 (2%)		1 (2%)
Pigmentation, hemosiderin	1 (2%)	1 (2%)		
Thrombosis			1 (2%)	
Bile duct, hyperplasia	4 (8%)	3 (6%)	3 (6%)	1 (2%)
Hepatocyte, hyperplasia	4 (8%)	6 (11%)	3 (6%)	8 (15%)
Hepatocyte, necrosis	6 (11%)	7 (13%)	3 (6%)	4 (7%)
Portal vein, thrombosis			1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(52)	(53)	(53)	(54)
Atrophy		2 (4%)	1 (2%)	
Acinus, atrophy	1 (2%)			
Artery, mineralization			1 (2%)	
Stomach, forestomach	(52)	(53)	(53)	(54)
Edema	1 (2%)			
Hyperkeratosis	1 (2%)	1 (2%)	4 (8%)	4 (7%)
Inflammation, chronic	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic active			1 (2%)	
Mineralization			1 (2%)	
Ulcer		3 (6%)	2 (4%)	1 (2%)
Stomach, glandular	(52)	(53)	(53)	(54)
Erosion		1 (2%)	1 (2%)	
Mineralization			1 (2%)	
Ulcer		1 (2%)		
Tooth	(1)			(1)
Inflammation, suppurative				1 (100%)
Cardiovascular System				
Blood vessel	(3)	(1)	(2)	
Aorta, mineralization			1 (50%)	
Aorta, polyarteritis		1 (100%)		
Mesenteric artery, polyarteritis		1 (100%)		
Mesenteric artery, thrombosis		1 (100%)		
Vena cava, mineralization			1 (50%)	
Heart	(53)	(53)	(53)	(54)
Inflammation, chronic				1 (2%)
Atrium, thrombosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Vein, inflammation, chronic active	1 (2%)			
Ventricle, mineralization			1 (2%)	
Endocrine System				
Adrenal cortex	(53)	(53)	(53)	(54)
Angiectasis	1 (2%)	3 (6%)	3 (6%)	
Atrophy	1 (2%)			
Congestion	1 (2%)	2 (4%)	2 (4%)	4 (7%)
Cyst	1 (2%)			
Degeneration	2 (4%)			
Degeneration, fatty	2 (4%)	3 (6%)	5 (9%)	8 (15%)
Edema			1 (2%)	1 (2%)
Hemorrhage	1 (2%)		1 (2%)	
Hyperplasia		1 (2%)	1 (2%)	
Bilateral, angiectasis		1 (2%)		
Adrenal medulla	(51)	(52)	(53)	(53)
Angiectasis	3 (6%)	1 (2%)		1 (2%)
Congestion		1 (2%)		
Hyperplasia	8 (16%)	12 (23%)	14 (26%)	22 (42%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Endocrine System (continued)				
Islets, pancreatic	(52)	(53)	(53)	(54)
Hyperplasia		1 (2%)		1 (2%)
Parathyroid gland	(47)	(47)	(50)	(50)
Cyst		1 (2%)		
Hyperplasia			1 (2%)	
Pituitary gland	(52)	(52)	(52)	(54)
Angiectasis	1 (2%)	1 (2%)		
Pars distalis, angiectasis	7 (13%)	6 (12%)	6 (12%)	5 (9%)
Pars distalis, cyst	8 (15%)	8 (15%)	11 (21%)	9 (17%)
Pars distalis, degeneration		1 (2%)		
Pars distalis, hemorrhage				2 (4%)
Pars distalis, hyperplasia	9 (17%)	11 (21%)	6 (12%)	12 (22%)
Pars intermedia, angiectasis		1 (2%)	1 (2%)	
Pars intermedia, cyst		1 (2%)		
Pars intermedia, hypertrophy		1 (2%)		
Thyroid gland	(52)	(52)	(53)	(53)
C-cell, hyperplasia			3 (6%)	2 (4%)
General Body System				
Tissue NOS	(6)	(1)	(3)	(3)
Abscess				1 (33%)
Genital System				
Clitoral gland	(53)	(53)	(51)	(50)
Atrophy	1 (2%)			
Ectasia	5 (9%)	3 (6%)	5 (10%)	4 (8%)
Hyperplasia, cystic		1 (2%)		
Inflammation, chronic active		1 (2%)		
Inflammation, suppurative		1 (2%)	1 (2%)	
Duct, ectasia				1 (2%)
Ovary	(53)	(53)	(53)	(54)
Cyst	5 (9%)	5 (9%)	7 (13%)	3 (6%)
Fibrosis				1 (2%)
Hemorrhage				1 (2%)
Bilateral, cyst				1 (2%)
Uterus	(53)	(53)	(52)	(54)
Cyst			1 (2%)	
Dilatation		1 (2%)		1 (2%)
Prolapse			1 (2%)	
Endometrium, hyperplasia, cystic	5 (9%)	1 (2%)	2 (4%)	7 (13%)
Hematopoietic System				
Bone marrow	(52)	(53)	(53)	(54)
Fibrosis	5 (10%)	3 (6%)	3 (6%)	1 (2%)
Hyperplasia	14 (27%)	15 (28%)	15 (28%)	16 (30%)
Necrosis		1 (2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node	(14)	(6)	(9)	(3)
Hyperplasia, lymphoid		1 (17%)		
Pigmentation	1 (7%)			
Iliac, hyperplasia, lymphoid	1 (7%)			
Pancreatic, hyperplasia, lymphoid			1 (11%)	
Pancreatic, inflammation, chronic active	1 (7%)			
Popliteal, pigmentation	1 (7%)			
Renal, congestion		2 (33%)		
Renal, edema				1 (33%)
Renal, hyperplasia, lymphoid			1 (11%)	
Renal, pigmentation				1 (33%)
Renal, pigmentation, hemosiderin	1 (7%)			
Lymph node, bronchial	(49)	(50)	(53)	(52)
Congestion	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Edema		1 (2%)	1 (2%)	
Hyperplasia, lymphoid	1 (2%)	5 (10%)	20 (38%)	13 (25%)
Hyperplasia, macrophage		1 (2%)		1 (2%)
Pigmentation		43 (86%)	52 (98%)	47 (90%)
Pigmentation, hemosiderin	1 (2%)			
Lymph node, mandibular	(47)	(45)	(51)	(49)
Congestion		1 (2%)		
Hyperplasia, lymphoid	3 (6%)	2 (4%)	3 (6%)	3 (6%)
Pigmentation	2 (4%)			
Lymph node, mesenteric	(51)	(53)	(53)	(54)
Congestion	1 (2%)			
Hyperplasia, lymphoid				3 (6%)
Inflammation, chronic active	1 (2%)			
Pigmentation	4 (8%)	2 (4%)		3 (6%)
Lymph node, mediastinal	(48)	(46)	(48)	(50)
Congestion	1 (2%)	5 (11%)	7 (15%)	1 (2%)
Ectasia			1 (2%)	
Edema			1 (2%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)	9 (20%)	14 (29%)	14 (28%)
Hyperplasia, plasma cell	1 (2%)		1 (2%)	
Inflammation, chronic active	1 (2%)			
Pigmentation		34 (74%)	39 (81%)	44 (88%)
Pigmentation, hemosiderin			1 (2%)	
Spleen	(53)	(53)	(53)	(54)
Fibrosis	1 (2%)	3 (6%)	3 (6%)	1 (2%)
Hematopoietic cell proliferation		1 (2%)		
Hemorrhage			1 (2%)	
Hyperplasia				2 (4%)
Hyperplasia, lymphoid			1 (2%)	
Infarct	1 (2%)	1 (2%)		
Necrosis		1 (2%)		
Capsule, fibrosis			1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Integumentary System				
Mammary gland	(53)	(53)	(53)	(54)
Hyperplasia, glandular		1 (2%)		
Skin	(4)	(3)	(3)	(5)
Inflammation, suppurative		1 (33%)		
Subcutaneous tissue, edema		1 (33%)		
Subcutaneous tissue, fibrosis			1 (33%)	
Musculoskeletal System				
Bone	(53)	(53)	(53)	(54)
Hyperostosis			2 (4%)	
Osteopetrosis	4 (8%)	2 (4%)		
Femur, hyperostosis	5 (9%)	2 (4%)	10 (19%)	8 (15%)
Skeletal muscle	(1)			
Inflammation, chronic	1 (100%)			
Nervous System				
Brain	(53)	(53)	(53)	(54)
Hemorrhage	1 (2%)			
Cerebellum, compression		1 (2%)	1 (2%)	
Cerebrum, compression	5 (9%)	4 (8%)	3 (6%)	5 (9%)
Cerebrum, ventricle, dilatation			2 (4%)	5 (9%)
Hypothalamus, compression	2 (4%)	1 (2%)	3 (6%)	5 (9%)
Pons, compression			1 (2%)	
Ventricle, dilatation	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Respiratory System				
Larynx	(53)	(53)	(53)	(54)
Inflammation, chronic	4 (8%)		2 (4%)	3 (6%)
Inflammation, chronic active	3 (6%)	2 (4%)	2 (4%)	
Inflammation, suppurative		1 (2%)	2 (4%)	
Lung	(53)	(53)	(53)	(54)
Congestion	1 (2%)		1 (2%)	1 (2%)
Cyst				1 (2%)
Hemorrhage			2 (4%)	2 (4%)
Inflammation, chronic	18 (34%)	52 (98%)	53 (100%)	54 (100%)
Inflammation, chronic active	1 (2%)			
Mineralization			1 (2%)	
Alveolar epithelium, hyperplasia, atypical	1 (2%)	1 (2%)	6 (11%)	5 (9%)
Alveolar epithelium, hyperplasia, focal	1 (2%)			1 (2%)
Alveolus, pigmentation		52 (98%)	53 (100%)	54 (100%)
Pleura, fibrosis			1 (2%)	
Nose	(53)	(53)	(52)	(54)
Inflammation, chronic		1 (2%)		1 (2%)
Inflammation, chronic active	1 (2%)			
Inflammation, suppurative		1 (2%)	2 (4%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
2-Year Study (continued)				
Respiratory System (continued)				
Trachea	(53)	(53)	(53)	(54)
Inflammation, chronic active			2 (4%)	
Inflammation, suppurative			2 (4%)	
Special Senses System				
Eye	(3)	(2)	(5)	(3)
Cataract			2 (40%)	2 (67%)
Hemorrhage	1 (33%)			
Inflammation, suppurative	1 (33%)			
Necrosis	1 (33%)			
Synechia			1 (20%)	
Bilateral, cornea, edema			1 (20%)	
Cornea, edema			2 (40%)	
Lens, cataract	1 (33%)			
Urinary System				
Kidney	(53)	(53)	(53)	(54)
Cyst			2 (4%)	
Nephropathy	36 (68%)	43 (81%)	35 (66%)	40 (74%)
Cortex, inflammation, chronic	1 (2%)	1 (2%)		
Cortex, necrosis, acute	1 (2%)			
Pelvis, cyst				1 (2%)
Pelvis, dilatation			1 (2%)	
Urinary bladder	(52)	(53)	(53)	(54)
Calculus, microscopic observation only			1 (2%)	
Edema			1 (2%)	

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF NICKEL OXIDE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
Disposition Summary				
Animals initially in study	78	77	76	79
7-Month interim evaluation	5	5	5	5
15-Month interim evaluation	5	5	5	5
Early deaths				
Accidental deaths[b]	10			
Moribund	23	26	26	29
Natural deaths	15	18	11	17
Survivors				
Terminal sacrifice	19	23	29	23
Missexed	1			
Animals examined microscopically	67	77	76	79
7-Month Interim Evaluation				
Alimentary System				
Liver	(1)		(2)	
Hepatocellular adenoma	1 (100%)		2 (100%)	
Respiratory System				
Lung	(5)	(5)	(5)	(5)
Alveolar/bronchiolar adenoma	1 (20%)			
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
15-Month Interim Evaluation				
Alimentary System				
Liver	(5)	(5)	(5)	(5)
Hepatocellular carcinoma	1 (20%)	1 (20%)	1 (20%)	
Hepatocellular adenoma	1 (20%)	1 (20%)	2 (40%)	
Endocrine System				
Thyroid gland	(5)	(5)	(5)	(5)
Follicular cell adenoma	1 (20%)			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(5)	(5)	(5)	(5)
Alveolar/bronchiolar adenoma	1 (20%)			
Hepatocellular carcinoma, metastatic	1 (20%)			
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Esophagus	(56)	(67)	(66)	(69)
Squamous cell carcinoma		1 (1%)		
Intestine large, colon	(50)	(61)	(60)	(62)
Intestine large, cecum	(49)	(56)	(60)	(60)
Intestine small, duodenum	(51)	(53)	(56)	(58)
Adenoma			1 (2%)	
Intestine small, ileum	(51)	(49)	(55)	(57)
Liver	(57)	(67)	(66)	(69)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (1%)
Hemangiosarcoma	1 (2%)			2 (3%)
Hemangiosarcoma, multiple		1 (1%)		
Hepatocellular carcinoma	6 (11%)	13 (19%)	8 (12%)	13 (19%)
Hepatocellular carcinoma, multiple		3 (4%)	3 (5%)	2 (3%)
Hepatocellular adenoma	7 (12%)	5 (7%)	11 (17%)	9 (13%)
Hepatocellular adenoma, multiple	1 (2%)		2 (3%)	
Hepatocholangiocarcinoma				1 (1%)
Histiocytic sarcoma				1 (1%)
Mesentery	(1)	(1)		
Lipoma	1 (100%)			
Salivary glands	(57)	(67)	(66)	(69)
Stomach, forestomach	(54)	(63)	(65)	(67)
Squamous cell papilloma	1 (2%)	1 (2%)		1 (1%)
Tooth	(2)	(5)	(4)	(1)
Odontoma		1 (20%)	2 (50%)	1 (100%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
2-Year Study (continued)				
Cardiovascular System				
Heart	(57)	(67)	(66)	(69)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (1%)
Hepatocholangiocarcinoma, metastatic, liver				1 (1%)
Endocrine System				
Adrenal cortex	(57)	(67)	(65)	(69)
Adenoma	2 (4%)			1 (1%)
Capsule, adenoma	2 (4%)		1 (2%)	
Islets, pancreatic	(54)	(64)	(66)	(68)
Adenoma			1 (2%)	
Thyroid gland	(55)	(67)	(66)	(69)
Bilateral, follicular cell, adenoma		2 (3%)		
Follicular cell, adenoma	2 (4%)		2 (3%)	2 (3%)
General Body System				
Tissue NOS	(2)		(3)	(4)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (25%)
Hemangiosarcoma	1 (50%)			
Hepatocholangiocarcinoma, metastatic, liver				1 (25%)
Lipoma			1 (33%)	
Sarcoma				1 (25%)
Genital System				
Epididymis	(56)	(67)	(66)	(68)
Sarcoma	1 (2%)			
Prostate	(53)	(61)	(63)	(65)
Testes	(57)	(66)	(66)	(69)
Interstitial cell, adenoma			2 (3%)	
Hematopoietic System				
Bone marrow	(56)	(66)	(66)	(68)
Hemangiosarcoma, metastatic	1 (2%)			
Lymph node	(22)	(18)	(20)	(16)
Axillary, alveolar/bronchiolar carcinoma, metastatic, lung				1 (6%)
Lymph node, bronchial	(45)	(56)	(61)	(62)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Lymph node, mandibular	(47)	(57)	(63)	(60)
Lymph node, mesenteric	(45)	(55)	(56)	(63)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Lymph node, mediastinal	(18)	(19)	(21)	(25)
Hemangiosarcoma, metastatic			1 (5%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
2-Year Study (continued)				
Hematopoietic System (continued)				
Spleen	(56)	(67)	(66)	(69)
Hemangioma				1 (1%)
Hemangiosarcoma	1 (2%)	1 (1%)	2 (3%)	1 (1%)
Histiocytic sarcoma				1 (1%)
Thymus	(45)	(53)	(52)	(58)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma				1 (2%)
Integumentary System				
Skin	(16)	(23)	(24)	(27)
Hamartoma		1 (4%)		
Subcutaneous tissue, hemangioma		1 (4%)		
Musculoskeletal System				
Bone	(57)	(67)	(66)	(68)
Hemangiosarcoma, metastatic	1 (2%)			
Nervous System				
None				
Respiratory System				
Lung	(57)	(67)	(66)	(69)
Alveolar/bronchiolar adenoma	7 (12%)	5 (7%)	6 (9%)	11 (16%)
Alveolar/bronchiolar carcinoma	4 (7%)	9 (13%)	9 (14%)	5 (7%)
Alveolar/bronchiolar carcinoma, multiple		1 (1%)		1 (1%)
Hepatocellular carcinoma, metastatic		1 (1%)	3 (5%)	4 (6%)
Hepatocellular carcinoma, metastatic, liver		1 (1%)		
Hepatocholangiocarcinoma, metastatic, liver				1 (1%)
Histiocytic sarcoma				1 (1%)
Nose	(55)	(66)	(66)	(67)
Special Senses System				
Harderian gland		(1)	(2)	(3)
Adenoma		1 (100%)	2 (100%)	2 (67%)
Urinary System				
Kidney	(57)	(67)	(66)	(68)
Urinary bladder	(54)	(63)	(65)	(66)
Transitional epithelium, papilloma		1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m^3	1.25 mg/m^3	2.5 mg/m^3	5 mg/m^3
2-Year Study (continued)				
Systemic Lesions				
Multiple organs[c]	(57)	(67)	(66)	(69)
Histiocytic sarcoma				1 (1%)
Lymphoma malignant	2 (4%)	2 (3%)	2 (3%)	5 (7%)
Neoplasm Summary				
Total animals with primary neoplasms[d]				
7-Month interim evaluation	2		2	
15-Month interim evaluation	3	2	3	
2-Year study	29	37	40	44
Total primary neoplasms				
7-Month interim evaluation	2		2	
15-Month interim evaluation	4	2	3	
2-Year study	39	49	55	60
Total animals with benign neoplasms				
7-Month interim evaluation	2		2	
15-Month interim evaluation	2	1	2	
2-Year study	18	16	25	26
Total benign neoplasms				
7-Month interim evaluation	2		2	
15-Month interim evaluation	3	1	2	
2-Year study	23	18	31	28
Total animals with malignant neoplasms				
15-Month interim evaluation	1	1	1	
2-Year study	15	28	22	30
Total malignant neoplasms				
15-Month interim evaluation	1	1	1	
2-Year study	16	31	24	32
Total animals with metastatic neoplasms				
15-Month interim evaluation	1			
2-Year study	1	2	4	6
Total metastatic neoplasms				
15-Month interim evaluation	1			
2-Year study	2	2	4	15

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] No histopathologic examination was performed on these animals.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³

Number of Days on Study	0 0 4	1 6 2	1 6 2	1 6 2	2 9 0	3 4 1	3 9 2	4 3 0	4 7 0	5 0 8	5 1 0	5 1 2	5 5 9	5 5 9	5 5 9	5 8 4	5 9 0	5 9 3	5 9 9	6 0 1	6 0 2	6 0 3	6 0 7	6 2 9	6 2 9
Carcass ID Number	0 6 5	0 2 5	0 2 8	0 2 9	0 0 8	0 4 3	0 3 1	0 2 2	0 3 6	0 2 1	0 1 5	0 1 0	0 0 9	0 1 4	0 5 4	0 0 5	0 5 3	0 3 9	0 1 2	0 6 3	0 1 8	0 4 5	0 1 9	0 5 0	0 5 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	A	A	+	M	A	+	M	A	+	+	+	+	M	A	A	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	A	+	+	A	+	+	+	+	+	+	+	+	A	A	A	+	+	A	+	+	+	+	+
Intestine large, rectum	A	M	A	+	+	A	+	+	+	+	+	+	+	+	A	A	A	+	+	A	+	+	+	+	M
Intestine large, cecum	A	+	A	+	+	A	+	+	+	+	+	+	+	+	A	A	A	+	+	A	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	A	A	A	+	+	A	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	A	A	A	+	+	A	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	A	A	A	+	+	A	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X										
Hepatocellular carcinoma							X		X							X									
Hepatocellular adenoma																						X			
Hepatocellular adenoma, multiple																									
Mesentery																									
Lipoma																									
Pancreas	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+
Tooth																									+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	M	M	+	M	+	M	M	M	M	M	M	M	A	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								X	
General Body System																									
Tissue NOS																									
Hemangiosarcoma																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																								X	
Penis								+					+	+							+				
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³ (continued)

Number of Days on Study	6 3 7	6 4 3	6 4 3	6 5 3	6 6 0	6 6 6	6 7 5	6 8 9	6 9 4	6 9 7	7 1 3	7 1 3	7 3 2	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	0 0 2	0 5 2	0 7 0	0 6 2	0 0 1	0 1 3	0 0 4	0 3 4	0 4 8	0 2 6	0 4 1	0 6 8	0 4 2	0 0 3	0 0 7	0 3 2	0 3 5	0 4 6	0 4 7	0 6 0	0 1 6	0 2 6	0 2 0	0 2 4	0 3 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+
Intestine large, cecum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma								X					X									X			
Hepatocellular adenoma										X			X	X					X		X				
Hepatocellular adenoma, multiple																						X			
Mesentery																									+
Lipoma																									X
Pancreas	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																	X								
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Capsule, adenoma																			X						
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									X
General Body System																									
Tissue NOS	+																								
Hemangiosarcoma	X																								
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Sarcoma																									
Penis						+	+			+															
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m^3 (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	0 3 8	0 6 1	0 3 0	0 3 3	0 6 4	0 6 6	0 6 7	Total Tissues/ Tumors
Alimentary System								
Esophagus	+	+	+	+	+	+	+	56
Gallbladder	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	57
Hemangiosarcoma								1
Hepatocellular carcinoma								6
Hepatocellular adenoma				X				7
Hepatocellular adenoma, multiple								1
Mesentery								1
Lipoma								1
Pancreas	+	+	+	+	+	+	+	54
Salivary glands	+	+	+	+	+	+	+	57
Stomach, forestomach	+	+	+	+	+	+	+	54
Squamous cell papilloma								1
Stomach, glandular	+	+	+	+	+	+	+	55
Tooth							+	2
Cardiovascular System								
Heart	+	+	+	+	+	+	+	57
Endocrine System								
Adrenal cortex	+	+	+	+	+	+	+	57
Adenoma		X						2
Capsule, adenoma				X				2
Adrenal medulla	+	+	+	+	+	+	+	57
Islets, pancreatic	+	+	+	+	+	+	+	54
Parathyroid gland	+	+	+	+	+	M	+	37
Pituitary gland	+	+	+	+	+	+	+	56
Thyroid gland	+	+	+	+	+	+	+	55
Follicular cell, adenoma								2
General Body System								
Tissue NOS					+			2
Hemangiosarcoma								1
Genital System								
Epididymis	+	+	+	+	+	+	+	56
Sarcoma								1
Penis								7
Preputial gland	+	+	+	+	+	+	+	57
Prostate	+	+	+	+	+	+	+	53
Seminal vesicle	+	+	+	+	+	+	+	55
Testes	+	+	+	+	+	+	+	57

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³ (continued)

Number of Days on Study	0 4	1 2	1 2	1 2	2 0	3 1	3 2	4 0	4 0	5 8	5 0	5 2	5 9	5 9	5 9	5 4	5 0	5 3	5 9	6 1	6 2	6 3	6 7	6 9	6 9
Carcass ID Number	0 6 5	0 2 5	0 2 8	0 2 9	0 0 8	0 4 3	0 3 1	0 2 2	0 3 6	0 2 1	0 1 5	0 1 0	0 0 9	0 1 4	0 5 4	0 5 5	0 8 3	0 9 9	0 1 2	0 6 3	0 1 8	0 4 5	0 1 9	0 5 0	0 5 7
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic																									
Lymph node			+		+						+	+	+					+		+	+	+		+	+
Lymph node, bronchial	+	+	+	+	I	M	+	+	I	+	+	+	+	+	+	M	I	+	M	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	A	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	M	I	+	+	+	+	+	+	+	M
Lymph node, mediastinal	M	M	M	M	M	M	+	M	+	+	+	M	M	M	+	M	M	+	M	+	M	+	M	M	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	I	+	+	+	M	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Skin					+						+	+	+	+	+						+	+	+	+	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic																									
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	M	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						
Alveolar/bronchiolar carcinoma														X											
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Trachea	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra																									
Urinary bladder	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																	X								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³ (continued)

Number of Days on Study	6 3 7	6 4 3	6 4 3	6 5 3	6 6 0	6 6 6	6 7 5	6 8 9	6 9 4	6 9 7	7 1 3	7 1 3	7 3 2	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	0 0 2	0 5 2	0 7 0	0 6 2	0 0 1	0 1 3	0 0 4	0 3 4	0 4 8	0 2 6	0 4 1	0 6 8	0 4 2	0 0 3	0 0 7	0 3 2	0 3 5	0 4 6	0 4 7	0 6 0	0 0 6	0 1 6	0 2 0	0 2 4	0 3 7
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic	X																								
Lymph node			+		+	+	+	+	+	+		+					+			+				
Lymph node, bronchial	+	+	+	M	+	+	+	+	+	I	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	M	M	M	M	M	M	M	+	M	+	M	M	+	M	+	M	I	M	+	I	M	M	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X					
Thymus	+	M	+	M	+	M	+	+	+	+	M	+	+	+	+	M	M	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin		+				+	+			+		+													+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic	X																								
Skeletal muscle		+																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X		X		X							X		X	
Alveolar/bronchiolar carcinoma													X									X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra				+																					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant									X																

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m^3 (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	0 3 8	0 6 1	0 3 0	0 3 3	0 6 4	0 6 6	0 6 7	Total Tissues/ Tumors
Hematopoietic System								
Bone marrow	+	+	+	+	+	+	+	56
Hemangiosarcoma, metastatic								1
Lymph node			+					22
Lymph node, bronchial	I	+	+	M	+	+	I	45
Lymph node, mandibular	+	+	+	+	+	M	+	47
Lymph node, mesenteric	+	+	+	+	+	M	M	45
Lymph node, mediastinal	+	+	M	M	+	M	+	18
Spleen	+	+	+	+	+	+	+	56
Hemangiosarcoma								1
Thymus	+	+	+	+	+	+	+	45
Integumentary System								
Mammary gland	+	+	+	+	+	+	+	56
Skin								16
Musculoskeletal System								
Bone	+	+	+	+	+	+	+	57
Hemangiosarcoma, metastatic								1
Skeletal muscle								1
Nervous System								
Brain	+	+	+	+	+	+	+	57
Respiratory System								
Larynx	+	+	+	+	+	+	+	55
Lung	+	+	+	+	+	+	+	57
Alveolar/bronchiolar adenoma						X		7
Alveolar/bronchiolar carcinoma	X							4
Nose	+	+	+	+	+	+	+	55
Trachea	+	+	+	+	+	+	+	56
Special Senses System								
None								
Urinary System								
Kidney	+	+	+	+	+	+	+	57
Urethra							+	2
Urinary bladder	+	+	+	+	+	+	+	54
Systemic Lesions								
Multiple organs	+	+	+	+	+	+	+	57
Lymphoma malignant								2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³

Number of Days on Study	0 2 4	1 0 5	1 3 5	1 5 7	2 2 6	2 9 0	2 9 8	3 4 1	4 4 2	4 4 5	4 7 1	4 8 0	4 9 3	5 0 1	5 0 8	5 1 2	5 3 9	5 3 9	5 5 7	5 6 7	5 9 3	6 0 4	6 1 0	6 1 2	6 1 2
Carcass ID Number	1 9 0	1 8 0	1 9 1	1 9 9	2 1 2	2 0 6	2 2 1	1 7 4	2 4 0	2 1 6	2 2 3	2 1 8	2 1 4	1 8 5	2 3 9	2 6 8	1 1 3	2 3 0	1 8 2	2 0 9	2 0 0	2 0 2	2 0 3	1 6 9	2 1 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Gallbladder	+	A	A	A	+	+	+	A	+	A	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+
Intestine large, colon	+	A	A	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+
Intestine large, rectum	M	A	A	+	+	+	+	M	A	M	M	A	+	M	A	+	+	+	+	M	+	+	+	+	+
Intestine large, cecum	+	A	A	M	+	+	+	+	A	+	+	A	+	+	A	A	+	+	+	+	+	+	A	+	+
Intestine small, duodenum	M	A	A	+	+	+	+	A	A	A	A	A	+	+	A	A	+	+	+	+	+	+	A	+	+
Intestine small, jejunum	M	A	A	M	+	+	+	A	A	A	A	A	+	+	A	+	+	+	+	+	+	+	A	+	+
Intestine small, ileum	M	A	A	M	+	+	+	A	A	A	A	A	+	+	A	A	+	+	+	+	+	+	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple																									
Hepatocellular carcinoma								X	X							X		X						X	
Hepatocellular carcinoma, multiple										X															
Hepatocellular adenoma																									
Mesentery																									
Pancreas	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	+	+	+	A	+	+	+	+		A	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	A	+	+	+	+	+	A	+	+	+	+		A	+	+	+	+	+	+	+	+	+	+
Tooth																									
Odontoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	M	M	M	M	+	+	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis					+	+	+												+	+					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	6 1 6	6 2 6	6 3 7	6 4 3	6 4 4	6 4 9	6 6 9	6 7 5	6 7 6	6 7 9	6 8 3	6 9 2	6 9 4	7 0 6	7 1 7	7 1 7	7 2 6	7 2 6	7 2 8	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8
Carcass ID Number	1 8 7	1 6 2	2 2 6	1 9 2	1 9 6	2 2 5	1 7 5	1 8 9	1 7 2	2 3 4	2 0 1	2 3 3	1 7 3	2 2 8	1 9 4	2 3 1	2 1 0	2 3 8	2 3 5	1 6 3	2 2 9	1 6 1	1 6 6	1 7 6	1 7 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Gallbladder	+	A	+	+	+	+	+	+	M	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	M	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Intestine large, cecum	+	+	+	+	+	+	+	M	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	A	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple																X									
Hepatocellular carcinoma					X			X	X		X					X			X			X			
Hepatocellular carcinoma, multiple														X			X								
Hepatocellular adenoma		X											X								X				
Mesentery																							+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																							X		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																	+							+	
Odontoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Parathyroid gland	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis							+	+		+		+			+	+									
Preputial gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	1 1 8 4	1 1 8 6	1 1 9 5	2 2 0 5	2 2 1 9	2 2 3 6	2 3 3 7	1 1 6 4	1 1 6 5	1 1 7 7	1 1 7 9	1 1 8 3	1 1 8 8	2 2 0 4	2 2 2 0	2 2 2 2	2 2 2 4	Total Tissues/ Tumors
Alimentary System																		
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Squamous cell carcinoma																	X	1
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	61
Intestine large, rectum	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	M	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	56
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Hemangiosarcoma, multiple																		1
Hepatocellular carcinoma															X			13
Hepatocellular carcinoma, multiple																		3
Hepatocellular adenoma				X											X			5
Mesentery																		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Squamous cell papilloma																		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Tooth	+		+		+													5
Odontoma			X															1
Cardiovascular System																		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Endocrine System																		
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Parathyroid gland	+	M	+	M	+	+	+	+	+	M	+	M	M	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Bilateral, follicular cell, adenoma										X					X			2
General Body System																		
None																		
Genital System																		
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Penis																		11
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Prostate	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	61
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	0 2 4	1 0 5	1 3 5	1 5 7	2 2 6	2 9 0	2 9 8	3 4 1	4 4 2	4 4 5	4 7 1	4 8 0	4 9 3	5 0 1	5 0 8	5 1 2	5 3 9	5 3 9	5 5 7	5 6 7	5 9 3	6 0 4	6 1 0	6 1 2	6 1 2
Carcass ID Number	1 9 0	1 8 0	1 9 1	1 9 9	2 1 2	2 0 6	2 2 1	1 7 4	2 4 0	2 1 6	2 2 3	2 1 8	2 1 4	1 8 5	2 3 9	1 6 8	2 1 3	2 3 0	1 8 2	2 0 9	2 0 0	2 0 2	2 0 3	1 6 9	2 1 7
Hematopoietic System																									
Bone marrow	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+	+			+		+	+		+	+	+		+	+				+
Lymph node, bronchial	M	I	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	M	M	+
Lymph node, mesenteric	M	M	M	+	+	M	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	+	M	M	+	M	M	+	I
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Thymus	+	+	I		+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	I	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin					+	+		+										+	+	+	+			+	+
Hamartoma																									
Subcutaneous tissue, hemangioma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic																									
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra							+																+		
Urinary bladder	+	A	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma												X													
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant														X											

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
	1	2	3	4	4	4	6	7	7	7	8	9	9	0	1	1	2	2	2	3	3	3	3	3	3
	6	6	7	3	4	9	9	5	6	9	3	2	4	6	7	7	6	6	8	7	7	8	8	8	8
Carcass ID Number	1	1	2	1	1	2	1	1	1	2	2	2	1	2	1	2	2	2	2	1	2	1	1	1	1
	8	6	2	9	9	2	7	8	7	3	0	3	7	2	9	3	1	3	3	6	2	6	6	7	7
	7	2	6	2	6	5	5	9	2	4	1	3	3	8	4	1	0	8	5	3	9	1	6	6	8
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+	+		+	+					+			+				+						
Lymph node, bronchial	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	M	+	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	M	M	+	+	+	+	+	M	M	M	M	+	M	M	M	+	M	M	+	M	+	M	M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	M	+	+	+	+	M	+	M	I	+	+	I	+	+	M	I	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin			+	+			+	+	+	+	+	+			+	+	+		+			+		+	
Hamartoma										X															
Subcutaneous tissue, hemangioma																X									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X												X							
Alveolar/bronchiolar carcinoma	X			X				X		X						X						X		X	
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic																			X						
Hepatocellular carcinoma, metastatic, liver																	X								
Nose	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																				+					
Adenoma																				X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant						X																			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	1 8 4	1 8 6	1 9 5	2 0 5	2 1 9	2 3 6	2 3 7	1 6 4	1 6 5	1 7 7	1 7 9	1 8 3	1 8 8	2 0 4	2 2 0	2 2 2	2 2 4	Total Tissues/ Tumors
Hematopoietic System																		
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Lymph node																		18
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	56
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	57
Lymph node, mesenteric	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Lymph node, mediastinal	I	M	M	M	M	M	+	+	M	M	M	+	M	M	+	M	+	19
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Hemangiosarcoma																		1
Thymus	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	M	M	53
Integumentary System																		
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Skin																		23
Hamartoma																		1
Subcutaneous tissue, hemangioma																		1
Musculoskeletal System																		
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Nervous System																		
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Respiratory System																		
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Alveolar/bronchiolar adenoma									X						X			5
Alveolar/bronchiolar carcinoma														X	X			9
Alveolar/bronchiolar carcinoma, multiple											X							1
Hepatocellular carcinoma, metastatic																		1
Hepatocellular carcinoma, metastatic, liver																		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Special Senses System																		
Harderian gland																		1
Adenoma																		1
Urinary System																		
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Urethra															+	+		4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Transitional epithelium, papilloma																		1
Systemic Lesions																		
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Lymphoma malignant																		2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³

Number of Days on Study	1 5 5	2 4 5	3 5 6	3 6 8	4 6 3	4 8 2	4 8 3	4 8 3	4 8 9	5 1 6	5 3 9	5 3 9	5 3 9	5 4 0	5 5 2	6 8 0	6 0 3	6 0 5	6 2 9	6 4 8	6 4 9	6 6 0	6 6 0	6 6 5	6 6 5
Carcass ID Number	3 5 1	3 7 2	3 3 6	3 7 3	3 3 1	3 6 9	3 9 4	4 0 0	3 4 4	3 2 2	3 2 3	3 2 8	3 5 0	3 5 4	3 7 4	3 4 6	3 2 1	3 5 6	3 9 1	3 3 4	3 7 9	3 8 7	3 9 0	3 3 8	3 8 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	M	+	+	+	A	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	A	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	A	+	A	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+
Intestine large, cecum	+	A	+	A	+	+	+	+	+	A	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	A	+	+	+	A	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+
Adenoma																									
Intestine small, jejunum	A	A	+	A	+	+	+	A	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+
Intestine small, ileum	A	A	+	A	+	+	+	A	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma												X	X	X			X	X							
Hepatocellular carcinoma, multiple																								X	
Hepatocellular adenoma									X				X		X						X				
Hepatocellular adenoma, multiple						X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Odontoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Parathyroid gland	M	M	+	M	+	+	+	+	+	M	+	+	M	M	M	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS												+													
Lipoma																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis			+																	+		+	+		
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																					X				

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³ (continued)

Number of Days on Study	6 7 6	6 7 6	6 7 7	6 7 9	6 8 4	6 9 4	6 9 6	7 0 4	7 0 9	7 1 2	7 1 8	7 3 0	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	3 5 8	3 6 7	3 5 9	3 8 1	3 4 7	3 3 9	3 2 7	3 6 8	3 8 2	3 8 0	3 9 8	3 4 2	3 2 4	3 2 5	3 3 7	3 5 2	3 5 3	3 5 7	3 6 0	3 6 3	3 6 5	3 6 6	3 6 0	3 7 8	3 8 9	3 9 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	A	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	M	+	+	+	M	A	+	+	+	+	+	M	+	+	+	+	I	M	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Intestine small, jejunum	+	+	+	+	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	A	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma									X																	
Hepatocellular carcinoma, multiple				X															X							
Hepatocellular adenoma		X																			X	X				
Hepatocellular adenoma, multiple																										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth														+												
Odontoma																										
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																										
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Parathyroid gland	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma				X																X						
General Body System																										
Tissue NOS																			+							
Lipoma																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis	+				+	+																				
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³ (continued)

Number of Days on Study	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	3 9 5	3 2 9	3 3 0	3 3 3	3 4 0	3 4 5	3 6 2	3 7 5	3 7 7	3 8 6	3 9 6	3 2 6	3 3 5	3 4 3	3 4 8	3 5 5	Total Tissues/ Tumors
Alimentary System																	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	57
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Intestine large, rectum	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	56
Adenoma										X							1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	56
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Hepatocellular carcinoma						X						X					8
Hepatocellular carcinoma, multiple																	3
Hepatocellular adenoma				X	X		X									X	11
Hepatocellular adenoma, multiple			X														2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Tooth	+			+					+								4
Odontoma				X					X								2
Cardiovascular System																	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Endocrine System																	
Adrenal cortex	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	65
Capsule, adenoma								X									1
Adrenal medulla	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	65
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Adenoma																	1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	53
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	63
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Follicular cell, adenoma																	2
General Body System																	
Tissue NOS			+														3
Lipoma			X														1
Genital System																	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Penis																	7
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Interstitial cell, adenoma								X									2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³ (continued)

Number of Days on Study	1 5 5	2 4 5	3 5 6	3 6 8	4 6 3	4 8 2	4 8 3	4 8 3	4 8 9	5 1 6	5 3 9	5 3 9	5 3 9	5 4 0	5 5 2	5 8 0	6 0 3	6 0 5	6 2 9	6 4 8	6 4 9	6 6 0	6 6 0	6 6 5	6 6 5
Carcass ID Number	3 5 1	3 7 2	3 3 6	3 7 3	3 3 1	3 6 9	3 9 4	4 0 0	3 4 4	3 2 2	3 2 3	3 2 8	3 5 0	3 5 4	3 7 4	3 4 6	3 2 1	3 5 6	3 9 1	3 3 4	3 7 9	3 8 7	3 9 0	3 3 8	3 8 9
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+			+			+	+	+	+		+	+	+	+		+	+		+	+		
Lymph node, bronchial	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	+	M	+	M	+	+	I	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	M	M	M	M	M	M	M	+	+	+	M	M	M	M	M	M	M	+	M	M	M	M	+	+
Hemangiosarcoma, metastatic																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	I	M	+	+	+	+	+	M	+	+	I	+
Integumentary System																									
Mammary gland	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin									+		+	+	+		+	+			+	+		+	+		+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma							X																		
Hepatocellular carcinoma, metastatic												X												X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																					+				
Adenoma																					X				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter									+																
Urethra									+						+										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³ (continued)

Number of Days on Study	6 7 6	6 7 6	6 7 7	6 7 9	6 8 4	6 9 4	6 9 6	7 0 4	7 0 9	7 1 2	7 1 8	7 3 0	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	3 5 8	3 6 7	3 5 9	3 8 1	3 4 7	3 3 9	3 2 7	3 6 8	3 8 2	3 8 0	3 9 8	3 4 2	3 2 4	3 2 5	3 3 7	3 5 2	3 5 3	3 5 7	3 6 0	3 6 3	3 6 5	3 6 6	3 7 0	3 8 8	3 9 2
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+			+			+									+				+				
Lymph node, bronchial	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	M	M	M	+	M	+	M	M	M	+	M	M	I	+	+	M	+	+	M	M	+	+	M
Hemangiosarcoma, metastatic																			X					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																			X					
Thymus	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+
Skin	+	+	+	+	+		+	+			+			+		+	+								+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X						X						X		X		X	X							
Alveolar/bronchiolar carcinoma			X											X						X					
Hepatocellular carcinoma, metastatic									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Harderian gland																									+
Adenoma																									X
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter												+													
Urethra							+	+						+											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																				X					

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³ (continued)

Number of Days on Study	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	3 9 5	3 2 9	3 3 0	3 3 3	3 4 0	3 4 5	3 6 2	3 7 5	3 7 7	3 8 6	3 9 6	3 2 6	3 3 5	3 4 3	3 4 8	3 5 5	Total Tissues/ Tumors
Hematopoietic System																	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Lymph node												+					20
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	M	61
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	56
Lymph node, mediastinal	I	+	M	+	M	M	M	+	M	+	M	+	I	M	M	M	21
Hemangiosarcoma, metastatic																	1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Hemangiosarcoma				X													2
Thymus	+	I	+	M	+	M	+	+	+	M	+	M	+	+	+	+	52
Integumentary System																	
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Skin												+					24
Musculoskeletal System																	
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Nervous System																	
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Respiratory System																	
Larynx	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Alveolar/bronchiolar adenoma																	6
Alveolar/bronchiolar carcinoma		X			X			X			X		X				9
Hepatocellular carcinoma, metastatic																	3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Special Senses System																	
Harderian gland																	2
Adenoma																	2
Urinary System																	
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Ureter																	2
Urethra																	5
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Systemic Lesions																	
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Lymphoma malignant															X		2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³

Number of Days on Study	0 2 1	1 3 7	1 9 4	2 2 4	2 4 1	2 7 1	3 1 7	4 2 2	4 2 8	4 3 1	4 5 9	4 8 9	4 9 9	5 0 1	5 2 7	5 3 8	5 4 3	5 5 9	5 7 1	5 7 4	5 8 0	5 8 0	5 9 7	6 0 1	6 1 2
Carcass ID Number	4 9 9	5 0 1	4 8 6	5 4 6	4 9 5	5 2 6	5 5 7	5 2 8	5 2 2	5 3 4	5 2 0	5 1 7	5 1 6	5 4 0	4 9 0	5 4 8	4 4 5	5 4 4	5 4 1	5 3 6	5 0 0	5 3 2	5 4 9	5 2 9	5 6 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	M	+	+	+	+	A	+	+	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	A	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	A	+	+	A	+	A	+	+	+	M	+	A	+	+	+	+	M	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	A	+	A	+	+	A	+	M	A	+	+	+	+	M	+	+	+	M	+	+
Intestine small, duodenum	A	+	A	+	+	A	+	A	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	A	+	+	A	+	A	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	A	+	+	A	+	A	+	+	A	+	A	A	+	+	+	M	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Hemangiosarcoma																									
Hepatocellular carcinoma											X			X				X					X	X	
Hepatocellular carcinoma, multiple																				X					
Hepatocellular adenoma										X	X						X								
Hepatocholangiocarcinoma															X										
Histiocytic sarcoma								X																	
Pancreas	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Odontoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Hepatocholangiocarcinoma, metastatic, liver															X										
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	M	M	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS							+			+					+										
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Hepatocholangiocarcinoma, metastatic, liver															X										
Sarcoma							X																		

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³ (continued)

Number of Days on Study	6 1 5	6 1 6	6 3 5	6 4 1	6 5 9	6 5 9	6 7 0	6 7 0	6 7 6	6 9 7	6 9 8	6 9 8	6 9 8	7 0 4	7 0 6	7 1 3	7 1 4	7 1 6	7 2 6	7 2 6	7 3 6	7 3 7	7 3 7	7 3 7
Carcass ID Number	5 0 7	5 0 9	5 5 9	5 1 1	5 2 7	5 4 7	5 3 1	5 4 3	5 4 5	5 2 5	4 8 2	5 0 2	5 5 3	5 2 4	5 1 2	5 1 3	5 5 8	5 5 4	5 2 3	5 3 7	4 8 4	4 9 1	4 9 8	5 0 6	5 1 0
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	A	A	A	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	A	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung													X											
Hemangiosarcoma														X					X					
Hepatocellular carcinoma														X				X		X	X			
Hepatocellular carcinoma, multiple				X																				
Hepatocellular adenoma		X																X						
Hepatocholangiocarcinoma																								
Histiocytic sarcoma																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Stomach, glandular	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																								
Odontoma																								
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung													X											
Hepatocholangiocarcinoma, metastatic, liver																								
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X						
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								
General Body System																								
Tissue NOS													+											
Alveolar/bronchiolar carcinoma, metastatic, lung													X											
Hepatocholangiocarcinoma, metastatic, liver																								
Sarcoma																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³ (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	5 1 9	5 3 3	5 4 2	5 5 0	5 5 5	4 8 3	4 8 9	5 3 0	5 3 9	4 8 1	4 8 7	4 8 8	4 9 4	4 9 6	5 0 3	5 0 5	5 4 8	5 5 2	5 5 6	Total Tissues/ Tumors
Alimentary System																				
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Intestine large, rectum	+	+	+	M	+	M	M	+	+	+	+	M	M	M	+	M	M	+	M	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	57
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Alveolar/bronchiolar carcinoma, metastatic, lung																				1
Hemangiosarcoma																				2
Hepatocellular carcinoma		X							X		X							X		13
Hepatocellular carcinoma, multiple																				2
Hepatocellular adenoma	X	X	X								X									9
Hepatocholangiocarcinoma																				1
Histiocytic sarcoma																				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Squamous cell papilloma						X														1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Tooth					+															1
Odontoma					X															1
Cardiovascular System																				
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Alveolar/bronchiolar carcinoma, metastatic, lung																				1
Hepatocholangiocarcinoma, metastatic, liver																				1
Endocrine System																				
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Adenoma																				1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	57
Pituitary gland	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Follicular cell, adenoma																		X	X	2
General Body System																				
Tissue NOS																				4
Alveolar/bronchiolar carcinoma, metastatic, lung																				1
Hepatocholangiocarcinoma, metastatic, liver																				1
Sarcoma																				1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³ (continued)

Number of Days on Study	0 2 1	1 3 7	1 9 4	2 2 4	2 4 1	2 7 1	3 1 7	4 2 2	4 2 8	4 3 1	4 5 9	4 8 9	4 9 9	5 0 1	5 2 7	5 3 8	5 4 3	5 5 9	5 7 1	5 7 4	5 8 0	5 8 0	5 9 7	6 0 1	6 1 2
Carcass ID Number	4 9 9	5 0 1	4 8 6	5 4 6	4 9 5	5 2 6	5 5 7	5 2 8	5 2 2	5 3 4	5 2 0	5 1 7	5 1 6	5 4 0	4 9 0	5 0 8	4 8 5	5 4 4	5 5 1	5 3 6	5 0 0	5 3 2	5 4 9	5 2 9	5 5 0
Genital System																									
Epididymis	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis									+				+							+	+		+	+	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+	+			+	+		+				+	+				+
Axillary, alveolar/bronchiolar carcinoma, metastatic, lung																									
Lymph node, bronchial	M	+	M	+	M	+	M	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Hepatocholangiocarcinoma, metastatic, liver															X										
Lymph node, mandibular	+	+	M	+	+	+	+	A	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M
Lymph node, mesenteric	+	+	+	M	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver															X										
Lymph node, mediastinal	M	+	M	M	M	M	M	+	+	M	M	+	M	M	+	M	+	M	+	+	M	+	M	M	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma						X																			
Histiocytic sarcoma								X																	
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	I	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Hepatocholangiocarcinoma, metastatic, liver															X										
Histiocytic sarcoma								X																	
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin							+				+	+		+			+				+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X													
Alveolar/bronchiolar carcinoma																			X						
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic																		X		X					
Hepatocholangiocarcinoma, metastatic, liver															X										
Histiocytic sarcoma								X																	
Nose	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³ (continued)

Number of Days on Study	6 1 5	6 1 6	6 3 5	6 4 1	6 5 9	6 5 9	6 7 0	6 7 0	6 7 6	6 9 7	6 9 8	6 9 8	6 9 8	7 0 4	7 0 6	7 1 3	7 1 4	7 1 6	7 2 6	7 2 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	5 0 7	5 0 9	5 5 9	5 1 1	5 2 7	5 4 7	5 3 1	5 4 3	5 4 5	5 2 5	4 8 2	5 0 2	5 5 3	5 2 4	5 1 2	5 1 3	5 5 8	5 5 4	5 2 3	5 3 7	4 8 4	4 9 1	4 9 8	5 0 6	5 1 0
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis			+		+		+		+	+	+									+					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+					+				+	+	+			+									
Axillary, alveolar/bronchiolar carcinoma, metastatic, lung													X												
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Lymph node, mediastinal	+	+	+	+	M	+	M	+	+	M	+	+	M	+	M	I	M	M	+	M	+	M	I	M	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma													X												
Hemangiosarcoma																									
Histiocytic sarcoma																									
Thymus	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung													X												
Hepatocholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+		+		+				+				+			+	+	+	+	+			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X			X			X			X					X						X			
Alveolar/bronchiolar carcinoma													X									X			
Alveolar/bronchiolar carcinoma, multiple										X															
Hepatocellular carcinoma, metastatic				X																	X				
Hepatocholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³ (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	5 1 9	5 3 3	5 4 2	5 5 0	5 5 5	4 8 3	4 8 9	5 3 0	5 3 9	4 8 1	4 8 7	4 8 8	4 9 4	4 9 6	5 0 3	5 0 5	5 4 8	5 5 2	5 5 6	Total Tissues/ Tumors
Genital System																				
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Penis																				13
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	65
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Hematopoietic System																				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Lymph node																	+			16
Axillary, alveolar/bronchiolar carcinoma, metastatic, lung																				1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Hepatocholangiocarcinoma, metastatic, liver																				1
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	63
Hepatocholangiocarcinoma, metastatic, liver																				1
Lymph node, mediastinal	+	M	I	I	M	+	M	M	M	I	M	M	M	M	M	M	+	I	+	25
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Hemangioma																				1
Hemangiosarcoma																				1
Histiocytic sarcoma																				1
Thymus	+	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58
Alveolar/bronchiolar carcinoma, metastatic, lung																				1
Hepatocholangiocarcinoma, metastatic, liver																				1
Histiocytic sarcoma																				1
Integumentary System																				
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Skin								+			+			+	+		+			27
Musculoskeletal System																				
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Nervous System																				
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Respiratory System																				
Larynx	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	66
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Alveolar/bronchiolar adenoma			X			X							X				X			11
Alveolar/bronchiolar carcinoma			X				X													5
Alveolar/bronchiolar carcinoma, multiple																				1
Hepatocellular carcinoma, metastatic																				4
Hepatocholangiocarcinoma, metastatic, liver																				1
Histiocytic sarcoma																				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	67
Trachea	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m^3 (continued)

Number of Days on Study	0	1	1	2	2	2	3	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	6	6
	2	3	9	2	4	7	1	2	2	3	5	8	9	0	2	3	4	5	7	7	8	8	9	0	1
	1	7	4	4	1	1	7	2	8	1	9	9	9	1	7	8	3	9	1	4	0	0	7	1	2
Carcass ID Number	4	5	4	5	4	5	5	5	5	5	5	5	5	5	4	5	4	5	5	5	5	5	5	5	5
	9	0	8	4	9	2	5	2	2	3	2	1	1	4	9	0	8	4	4	3	0	3	4	2	6
	9	1	6	6	5	6	7	8	2	4	0	7	6	0	0	8	5	4	1	6	0	2	9	9	0
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter														+					+				+		
Urethra						+						+				+			+	+					
Urinary bladder	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Lymphoma malignant		X																							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m^3 (continued)

Number of Days on Study	6 1 5	6 1 6	6 3 5	6 4 1	6 5 9	6 5 9	6 7 0	6 7 0	6 7 6	6 9 7	6 9 8	6 9 8	6 9 8	7 0 4	7 0 6	7 1 3	7 1 4	7 1 6	7 2 6	7 2 6	7 3 6	7 3 7	7 3 7	7 3 7
Carcass ID Number	5 0 7	5 0 9	5 5 9	5 1 1	5 2 7	5 4 7	5 3 1	5 4 3	5 4 5	5 2 5	4 8 2	5 0 2	5 5 3	5 2 4	5 1 2	5 1 3	5 5 8	5 5 4	5 2 3	5 3 7	4 8 4	4 9 1	4 9 8	5 0 6	5 1 0
Special Senses System																									
Harderian gland																	+								
Adenoma																	X								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter												+													
Urethra		+	+												+				+						
Urinary bladder	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant	X					X						X													

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³ (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	5 1 9	5 3 3	5 4 2	5 5 0	5 5 5	4 8 3	4 8 9	5 3 0	5 3 9	4 8 1	4 8 7	4 8 8	4 9 4	4 9 6	5 0 3	5 0 5	5 4 8	5 5 2	5 5 6	Total Tissues/ Tumors
Special Senses System																				
Harderian gland		+		+																3
Adenoma				X																2
Urinary System																				
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Ureter																				4
Urethra													+	+	+					12
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Systemic Lesions																				
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Histiocytic sarcoma																				1
Lymphoma malignant																	X			5

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Oxide

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
Adrenal Cortex: Adenoma				
Overall rate[a]	4/57 (7%)	0/67 (0%)	1/65 (2%)	1/69 (1%)
Adjusted rate[b]	21.1%	0.0%	3.6%	3.7%
Terminal rate[c]	4/19 (21%)	0/23 (0%)	1/28 (4%)	0/23 (0%)
First incidence (days)	737 (T)	—[e]	737 (T)	716
Life table test[d]	P=0.122N	P=0.039N	P=0.079N	P=0.120N
Logistic regression test[d]	P=0.113N	P=0.039N	P=0.079N	P=0.101N
Cochran-Armitage test[d]	P=0.137N			
Fisher exact test[d]		P=0.042N	P=0.144N	P=0.129N
Liver: Hepatocellular Adenoma				
Overall rate	8/57 (14%)	5/67 (7%)	13/66 (20%)	9/69 (13%)
Adjusted rate	34.9%	18.0%	32.6%	26.4%
Terminal rate	5/19 (26%)	3/23 (13%)	7/29 (24%)	4/23 (17%)
First incidence (days)	603	626	482	431
Life table test	P=0.432	P=0.167N	P=0.491	P=0.522N
Logistic regression test	P=0.426	P=0.154N	P=0.364	P=0.520N
Cochran-Armitage test	P=0.404			
Fisher exact test		P=0.185N	P=0.278	P=0.537N
Liver: Hepatocellular Carcinoma				
Overall rate	6/57 (11%)	16/67 (24%)	11/66 (17%)	15/69 (22%)
Adjusted rate	19.0%	37.8%	24.9%	39.5%
Terminal rate	1/19 (5%)	2/23 (9%)	3/29 (10%)	5/23 (22%)
First incidence (days)	392	341	539	459
Life table test	P=0.212	P=0.073	P=0.379	P=0.095
Logistic regression test	P=0.155	P=0.044	P=0.233	P=0.077
Cochran-Armitage test	P=0.170			
Fisher exact test		P=0.043	P=0.236	P=0.073
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	12/57 (21%)	20/67 (30%)	23/66 (35%)	20/69 (29%)
Adjusted rate	41.4%	46.9%	50.3%	49.3%
Terminal rate	5/19 (26%)	4/23 (17%)	10/29 (34%)	7/23 (30%)
First incidence (days)	392	341	482	431
Life table test	P=0.308	P=0.247	P=0.240	P=0.246
Logistic regression test	P=0.237	P=0.181	P=0.092	P=0.216
Cochran-Armitage test	P=0.246			
Fisher exact test		P=0.182	P=0.067	P=0.209
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	7/57 (12%)	5/67 (7%)	6/66 (9%)	11/69 (16%)
Adjusted rate	30.2%	16.2%	18.3%	33.0%
Terminal rate	4/19 (21%)	2/23 (9%)	4/29 (14%)	5/23 (22%)
First incidence (days)	599	512	676	489
Life table test	P=0.206	P=0.259N	P=0.221N	P=0.409
Logistic regression test	P=0.196	P=0.255N	P=0.242N	P=0.403
Cochran-Armitage test	P=0.179			
Fisher exact test		P=0.274N	P=0.388N	P=0.374

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	4/57 (7%)	10/67 (15%)	9/66 (14%)	6/69 (9%)
Adjusted rate	16.9%	32.4%	27.3%	19.6%
Terminal rate	2/19 (11%)	5/23 (22%)	7/29 (24%)	3/23 (13%)
First incidence (days)	559	616	483	571
Life table test	P=0.449N	P=0.160	P=0.321	P=0.520
Logistic regression test	P=0.444N	P=0.141	P=0.263	P=0.520
Cochran-Armitage test	P=0.485N			
Fisher exact test		P=0.135	P=0.186	P=0.497
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	9/57 (16%)	14/67 (21%)	15/66 (23%)	14/69 (20%)
Adjusted rate	36.3%	41.4%	43.6%	39.7%
Terminal rate	5/19 (26%)	6/23 (26%)	11/29 (38%)	6/23 (26%)
First incidence (days)	559	512	483	489
Life table test	P=0.404	P=0.355	P=0.467	P=0.381
Logistic regression test	P=0.393	P=0.322	P=0.380	P=0.364
Cochran-Armitage test	P=0.353			
Fisher exact test		P=0.311	P=0.230	P=0.339
All Organs: Hemangiosarcoma				
Overall rate	3/57 (5%)	2/67 (3%)	2/66 (3%)	3/69 (4%)
Adjusted rate	10.3%	5.7%	6.9%	8.4%
Terminal rate	1/19 (5%)	0/23 (0%)	2/29 (7%)	0/23 (0%)
First incidence (days)	559	604	737 (T)	271
Life table test	P=0.545N	P=0.404N	P=0.343N	P=0.552N
Logistic regression test	P=0.554N	P=0.425N	P=0.385N	P=0.572N
Cochran-Armitage test	P=0.559N			
Fisher exact test		P=0.423N	P=0.431N	P=0.565N
All Organs: Hemangiosarcoma or Hemangioma				
Overall rate	3/57 (5%)	2/67 (3%)	2/66 (3%)	4/69 (6%)
Adjusted rate	10.3%	5.7%	6.9%	11.1%
Terminal rate	1/19 (5%)	0/23 (0%)	2/29 (7%)	0/23 (0%)
First incidence (days)	559	604	737 (T)	271
Life table test	P=0.453	P=0.404N	P=0.343N	P=0.634
Logistic regression test	P=0.435	P=0.425N	P=0.385N	P=0.604
Cochran-Armitage test	P=0.429			
Fisher exact test		P=0.423N	P=0.431N	P=0.606
All Organs: Malignant Lymphoma				
Overall rate	2/57 (4%)	2/67 (3%)	2/66 (3%)	5/69 (7%)
Adjusted rate	6.5%	4.5%	6.9%	12.8%
Terminal rate	0/19 (0%)	0/23 (0%)	2/29 (7%)	1/23 (4%)
First incidence (days)	590	501	737 (T)	137
Life table test	P=0.177	P=0.626N	P=0.558N	P=0.346
Logistic regression test	P=0.156	P=0.635N	P=0.594N	P=0.299
Cochran-Armitage test	P=0.156			
Fisher exact test		P=0.627N	P=0.633N	P=0.306

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m^3	1.25 mg/m^3	2.5 mg/m^3	5 mg/m^3
All Organs: Benign Neoplasms				
Overall rate	19/57 (33%)	17/67 (25%)	26/66 (39%)	26/69 (38%)
Adjusted rate	71.4%	50.0%	61.9%	67.1%
Terminal rate	12/19 (63%)	8/23 (35%)	15/29 (52%)	12/23 (52%)
First incidence (days)	599	480	482	431
Life table test	P=0.221	P=0.183N	P=0.458N	P=0.434
Logistic regression test	P=0.190	P=0.176N	P=0.495	P=0.416
Cochran-Armitage test	P=0.169			
Fisher exact test		P=0.219N	P=0.306	P=0.375
All Organs: Malignant Neoplasms				
Overall rate	15/57 (26%)	28/67 (42%)	23/66 (35%)	30/69 (43%)
Adjusted rate	43.3%	60.7%	54.0%	61.9%
Terminal rate	4/19 (21%)	7/23 (30%)	12/29 (41%)	8/23 (35%)
First incidence (days)	392	341	483	137
Life table test	P=0.136	P=0.111	P=0.471	P=0.080
Logistic regression test	P=0.070	P=0.039	P=0.267	P=0.035
Cochran-Armitage test	P=0.072			
Fisher exact test		P=0.053	P=0.205	P=0.034
All Organs: Benign or Malignant Neoplasms				
Overall rate	30/57 (53%)	37/67 (55%)	40/66 (61%)	44/69 (64%)
Adjusted rate	84.1%	76.0%	85.8%	81.5%
Terminal rate	14/19 (74%)	12/23 (52%)	23/29 (79%)	14/23 (61%)
First incidence (days)	392	341	482	137
Life table test	P=0.214	P=0.538	P=0.392N	P=0.258
Logistic regression test	P=0.110	P=0.455	P=0.434	P=0.145
Cochran-Armitage test	P=0.099			
Fisher exact test		P=0.457	P=0.239	P=0.140

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, and lung; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C4a
Historical Incidence of Alveolar/bronchiolar Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Lovelace Inhalation Toxicology Research Institute			
Nickel Oxide	7/57	4/57	9/57
Nickel Subsulfide	6/61	7/61	13/61
Nickel Sulfate Hexahydrate	5/61	9/61	13/61
Talc	6/45	7/45	12/45
Overall Historical Incidence in Inhalation Studies			
Total	141/952 (14.8%)	75/952 (7.9%)	205/952 (21.5%)
Standard deviation	7.0%	5.7%	8.0%
Range	6%-36%	0%-16%	10%-42%
Overall Historical Incidence in Feed Studies			
Total	194/1,319 (14.7%)	64/1,319 (4.9%)	249/1,319 (18.9%)
Standard deviation	6.4%	3.9%	7.6%
Range	4%-28%	0%-14%	4%-32%

[a] Data as of 17 June 1994

TABLE C4b
Historical Incidence of Hepatocellular Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Lovelace Inhalation Toxicology Research Institute			
Nickel Oxide	8/57	6/57	12/57
Nickel Subsulfide	13/61	11/61	24/61
Nickel Sulfate Hexahydrate	18/61	11/61	27/61
Talc	3/45	6/45	9/45
Overall Historical Incidence in Inhalation Studies			
Total	201/952 (21.1%)	185/952 (19.4%)	360/952 (37.8%)
Standard deviation	11.7%	5.8%	12.6%
Range	4%-46%	9%-29%	11%-60%
Overall Historical Incidence in Feed Studies			
Total	344/1,316 (26.1%)	220/1,316 (16.7%)	509/1,316 (38.7%)
Standard deviation	13.2%	7.2%	13.9%
Range	4%-60%	3%-29%	10%-68%

[a] Data as of 17 June 1994

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
Disposition Summary				
Animals initially in study	78	77	76	79
7-Month interim evaluation	5	5	5	5
15-Month interim evaluation	5	5	5	5
Early Deaths				
Accidental deaths[b]	10			
Moribund	23	26	26	29
Natural deaths	15	18	11	17
Survivors				
Terminal sacrifice	19	23	29	23
Missexed	1			
Animals examined microscopically	67	77	76	79
7-Month Interim Evaluation				
Genital System				
Preputial gland		(3)	(1)	(2)
Atrophy		1 (33%)		
Duct, concretion			1 (100%)	2 (100%)
Duct, ectasia		3 (100%)		
Hematopoietic System				
Lymph node		(1)		
Renal, pigmentation		1 (100%)		
Lymph node, bronchial	(4)	(3)	(5)	(4)
Hyperplasia, lymphoid			1 (20%)	
Pigmentation		2 (67%)	5 (100%)	4 (100%)
Respiratory System				
Lung	(5)	(5)	(5)	(5)
Inflammation, chronic		2 (40%)	3 (60%)	3 (60%)
Alveolus, pigmentation		5 (100%)	5 (100%)	5 (100%)
Urinary System				
Kidney	(5)	(5)	(5)	(5)
Infiltration cellular, lymphocyte		1 (20%)	1 (20%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m^3	1.25 mg/m^3	2.5 mg/m^3	5 mg/m^3
7-Month Interim Evaluation				
Systems Examined With No Lesions Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
15-Month Interim Evaluation				
Alimentary System				
Liver	(5)	(5)	(5)	(5)
Basophilic focus		1 (20%)		
Eosinophilic focus				1 (20%)
Salivary glands	(5)	(5)	(5)	(5)
Infiltration cellular, lymphocyte	1 (20%)			
Genital System				
Penis	(1)			
Inflammation, suppurative	1 (100%)			
Preputial gland	(5)	(5)	(5)	(5)
Ectasia	4 (80%)	5 (100%)	3 (60%)	2 (40%)
Inflammation, suppurative	1 (20%)	1 (20%)		
Hematopoietic System				
Lymph node	(1)			
Inguinal, hyperplasia, lymphoid	1 (100%)			
Renal, hyperplasia, lymphoid	1 (100%)			
Lymph node, bronchial	(5)	(5)	(5)	(5)
Hyperplasia, lymphoid			2 (40%)	4 (80%)
Pigmentation		4 (80%)	5 (100%)	5 (100%)
Spleen	(5)	(5)	(5)	(5)
Hyperplasia, lymphoid	2 (40%)		1 (20%)	
Respiratory System				
Lung	(5)	(5)	(5)	(5)
Inflammation, chronic	1 (20%)		2 (40%)	4 (80%)
Bronchialization[c]		1 (20%)		2 (40%)
Alveolar epithelium, hyperplasia, focal	1 (20%)			
Alveolus, pigmentation		5 (100%)	5 (100%)	5 (100%)
Alveolus, proteinosis			1 (20%)	3 (60%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m^3	1.25 mg/m^3	2.5 mg/m^3	5 mg/m^3
15-Month Interim Evaluation (continued)				
Urinary System				
Urinary bladder	(5)	(5)	(4)	(5)
Calculus, microscopic observation only	1 (20%)			
Systems Examined With No Lesions Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Gallbladder	(47)	(55)	(57)	(58)
Inflammation, chronic				1 (2%)
Necrosis			1 (2%)	
Intestine large, cecum	(49)	(56)	(60)	(60)
Hyperplasia, lymphoid				2 (3%)
Inflammation, chronic			1 (2%)	
Intestine small, ileum	(51)	(49)	(55)	(57)
Inflammation, suppurative	1 (2%)			
Ulcer	1 (2%)			
Liver	(57)	(67)	(66)	(69)
Abscess				1 (1%)
Angiectasis		1 (1%)		
Basophilic focus	1 (2%)	2 (3%)	3 (5%)	1 (1%)
Clear cell focus			1 (2%)	
Congestion			1 (2%)	
Cyst	1 (2%)		1 (2%)	
Developmental malformation				1 (1%)
Eosinophilic focus		1 (1%)		1 (1%)
Fatty change				1 (1%)
Hematopoietic cell proliferation				1 (1%)
Hepatodiaphragmatic nodule		1 (1%)		
Hyperplasia, macrophage	1 (2%)			
Infarct		6 (9%)	1 (2%)	4 (6%)
Inflammation, suppurative			1 (2%)	
Mixed cell focus		1 (1%)	1 (2%)	
Thrombosis		3 (4%)	1 (2%)	
Bile duct, cyst			1 (2%)	
Hepatocyte, cytomegaly	1 (2%)		1 (2%)	
Hepatocyte, cytoplasmic alteration	1 (2%)			
Hepatocyte, hyperplasia		1 (1%)		2 (3%)
Hepatocyte, necrosis	5 (9%)	2 (3%)	4 (6%)	4 (6%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
2-Year Study *(continued)*				
Alimentary System (continued)				
Mesentery	(1)	(1)		
Hemorrhage		1 (100%)		
Thrombosis		1 (100%)		
Vein, inflammation, chronic		1 (100%)		
Pancreas	(54)	(65)	(66)	(68)
Cyst				1 (1%)
Inflammation, chronic	1 (2%)			
Inflammation, chronic active		1 (2%)		
Stomach, forestomach	(54)	(63)	(65)	(67)
Hyperkeratosis		1 (2%)	1 (2%)	1 (1%)
Stomach, glandular	(55)	(63)	(65)	(67)
Inflammation, chronic		1 (2%)		
Inflammation, suppurative		1 (2%)	2 (3%)	1 (1%)
Tooth	(2)	(5)	(4)	(1)
Dysplasia	2 (100%)	4 (80%)	1 (25%)	1 (100%)
Peridontal tissue, inflammation, chronic active			1 (25%)	
Cardiovascular System				
Heart	(57)	(67)	(66)	(69)
Inflammation, chronic				1 (1%)
Inflammation, suppurative				1 (1%)
Atrium, thrombosis		1 (1%)		
Ventricle, thrombosis			1 (2%)	
Endocrine System				
Adrenal cortex	(57)	(67)	(65)	(69)
Cyst			1 (2%)	1 (1%)
Hyperplasia	6 (11%)	5 (7%)	6 (9%)	2 (3%)
Bilateral, hyperplasia		1 (1%)		
Bilateral, spindle cell, hyperplasia			1 (2%)	
Spindle cell, hyperplasia	1 (2%)	2 (3%)	1 (2%)	
Islets, pancreatic	(54)	(64)	(66)	(68)
Hyperplasia	2 (4%)		2 (3%)	
Parathyroid gland	(37)	(48)	(53)	(57)
Cyst	1 (3%)	1 (2%)		
Hyperplasia, cystic		2 (4%)		
Pituitary gland	(56)	(62)	(63)	(66)
Pars distalis, cyst		1 (2%)	1 (2%)	
Pars distalis, hyperplasia	2 (4%)	1 (2%)		1 (2%)
Thyroid gland	(55)	(67)	(66)	(69)
Hyperplasia, cystic	13 (24%)	27 (40%)	25 (38%)	27 (39%)
Inflammation, chronic		1 (1%)		
Inflammation, suppurative			1 (2%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
2-Year Study (continued)				
General Body System				
Tissue NOS	(2)		(3)	(4)
Abscess	1 (50%)			
Hemorrhage				1 (25%)
Inflammation, suppurative			1 (33%)	1 (25%)
Necrosis				1 (25%)
Necrosis, chronic			1 (33%)	
Genital System				
Epididymis	(56)	(67)	(66)	(68)
Granuloma sperm		1 (1%)	1 (2%)	
Inflammation, chronic	2 (4%)			2 (3%)
Inflammation, chronic active				1 (1%)
Inflammation, suppurative				1 (1%)
Penis	(7)	(11)	(7)	(13)
Concretion	1 (14%)	5 (45%)	5 (71%)	5 (38%)
Hemorrhage		1 (9%)	1 (14%)	
Inflammation		1 (9%)		1 (8%)
Inflammation, chronic	1 (14%)			
Inflammation, suppurative	5 (71%)	1 (9%)	1 (14%)	6 (46%)
Mineralization		1 (9%)		
Necrosis, chronic		1 (9%)	1 (14%)	
Preputial gland	(57)	(66)	(66)	(69)
Atrophy			4 (6%)	2 (3%)
Concretion		1 (2%)		
Ectasia	16 (28%)	17 (26%)	25 (38%)	20 (29%)
Hemorrhage		1 (2%)		
Inflammation, chronic	2 (4%)	7 (11%)	5 (8%)	9 (13%)
Inflammation, chronic active	9 (16%)	12 (18%)	7 (11%)	2 (3%)
Inflammation, suppurative	14 (25%)	8 (12%)	13 (20%)	11 (16%)
Bilateral, ectasia	23 (40%)	34 (52%)	37 (56%)	41 (59%)
Bilateral, inflammation, chronic active		2 (3%)	1 (2%)	
Bilateral, inflammation, suppurative			1 (2%)	
Prostate	(53)	(61)	(63)	(65)
Inflammation, chronic active		1 (2%)		
Inflammation, suppurative	1 (2%)	2 (3%)	1 (2%)	1 (2%)
Epithelium, hyperplasia		1 (2%)		
Seminal vesicle	(55)	(66)	(66)	(69)
Cyst				1 (1%)
Dilatation	1 (2%)	8 (12%)	11 (17%)	10 (14%)
Inflammation, chronic			1 (2%)	
Testes	(57)	(66)	(66)	(69)
Atrophy		3 (5%)	1 (2%)	1 (1%)
Congestion		1 (2%)		
Cyst		1 (2%)		
Inflammation, suppurative	1 (2%)			
Bilateral, atrophy				1 (1%)
Germinal epithelium, degeneration				1 (1%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(56)	(66)	(66)	(68)
Erythroid cell, hyperplasia				1 (1%)
Myeloid cell, hyperplasia	5 (9%)	13 (20%)	15 (23%)	13 (19%)
Myeloid cell, inflammation				1 (1%)
Lymph node	(22)	(18)	(20)	(16)
Iliac, hyperplasia, histiocytic	1 (5%)			
Iliac, hyperplasia, lymphoid	8 (36%)	8 (44%)	11 (55%)	8 (50%)
Iliac, inflammation, suppurative		1 (6%)		
Iliac, pigmentation		4 (22%)	3 (15%)	2 (13%)
Inguinal, hyperplasia	1 (5%)			
Inguinal, hyperplasia, lymphoid	12 (55%)	9 (50%)	11 (55%)	9 (56%)
Inguinal, pigmentation	1 (5%)	2 (11%)		
Pancreatic, hyperplasia, lymphoid			1 (5%)	
Pancreatic, inflammation, granulomatous	1 (5%)		1 (5%)	
Renal, hyperplasia, histiocytic	1 (5%)			
Renal, hyperplasia, lymphoid	2 (9%)	2 (11%)	1 (5%)	
Renal, pigmentation		1 (6%)		
Lymph node, bronchial	(45)	(56)	(61)	(62)
Atrophy		1 (2%)		
Congestion	1 (2%)		1 (2%)	1 (2%)
Edema		1 (2%)		1 (2%)
Hyperplasia, lymphoid	5 (11%)	18 (32%)	28 (46%)	33 (53%)
Inflammation, chronic active			1 (2%)	
Inflammation, granulomatous	1 (2%)			
Pigmentation		55 (98%)	61 (100%)	60 (97%)
Lymph node, mandibular	(47)	(57)	(63)	(60)
Hyperplasia, histiocytic		1 (2%)		
Hyperplasia, lymphoid	3 (6%)	3 (5%)	4 (6%)	2 (3%)
Lymph node, mesenteric	(45)	(55)	(56)	(63)
Congestion	4 (9%)	13 (24%)	12 (21%)	6 (10%)
Hematopoietic cell proliferation		1 (2%)		3 (5%)
Hyperplasia, lymphoid	3 (7%)	4 (7%)	5 (9%)	3 (5%)
Hyperplasia, macrophage			1 (2%)	
Inflammation, suppurative	4 (9%)	1 (2%)	2 (4%)	1 (2%)
Pigmentation		1 (2%)		
Lymph node, mediastinal	(18)	(19)	(21)	(25)
Congestion				2 (8%)
Hyperplasia, lymphoid	1 (6%)			
Inflammation, chronic			1 (5%)	
Pigmentation		3 (16%)	1 (5%)	1 (4%)
Spleen	(56)	(67)	(66)	(69)
Angiectasis		1 (1%)		
Hematopoietic cell proliferation	17 (30%)	14 (21%)	13 (20%)	17 (25%)
Hyperplasia, lymphoid	2 (4%)	5 (7%)	6 (9%)	4 (6%)
Thrombosis				2 (3%)
Thymus	(45)	(53)	(52)	(58)
Atrophy	1 (2%)	1 (2%)		1 (2%)
Cyst			1 (2%)	
Inflammation, granulomatous			1 (2%)	
Pigmentation		1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
2-Year Study (continued)				
Integumentary System				
Skin	(16)	(23)	(24)	(27)
Alopecia	1 (6%)	1 (4%)		1 (4%)
Cyst epithelial inclusion				1 (4%)
Inflammation, chronic		1 (4%)		
Inflammation, chronic active	1 (6%)	2 (9%)		1 (4%)
Inflammation, suppurative	13 (81%)	11 (48%)	16 (67%)	13 (48%)
Necrosis		2 (9%)	1 (4%)	1 (4%)
Prepuce, inflammation				1 (4%)
Prepuce, inflammation, chronic active			1 (4%)	
Prepuce, inflammation, suppurative		5 (22%)	3 (13%)	4 (15%)
Prepuce, necrosis			1 (4%)	
Subcutaneous tissue, edema		2 (9%)		
Subcutaneous tissue, fibrosis		1 (4%)		1 (4%)
Subcutaneous tissue, hemorrhage		1 (4%)		
Subcutaneous tissue, inflammation, chronic active			1 (4%)	
Subcutaneous tissue, inflammation, suppurative			1 (4%)	
Musculoskeletal System				
Bone	(57)	(67)	(66)	(68)
Developmental malformation			1 (2%)	
Fracture healed	2 (4%)	1 (1%)		1 (1%)
Hemorrhage		1 (1%)		
Hyperostosis	2 (4%)		4 (6%)	
Vertebra, inflammation, suppurative	1 (2%)			
Skeletal muscle	(1)			
Inflammation, suppurative	1 (100%)			
Nervous System				
Brain	(57)	(67)	(66)	(69)
Pons, demyelination		2 (3%)		
Respiratory System				
Lung	(57)	(67)	(66)	(69)
Congestion				1 (1%)
Fibrosis				1 (1%)
Hemorrhage		1 (1%)	2 (3%)	
Hyperplasia, macrophage		1 (1%)		
Inflammation, chronic		21 (31%)	34 (52%)	55 (80%)
Thrombosis		2 (3%)		
Bronchialization		24 (36%)	40 (61%)	40 (58%)
Alveolar epithelium, hyperplasia, focal	1 (2%)	1 (1%)	2 (3%)	
Alveolus, pigmentation		65 (97%)	66 (100%)	68 (99%)
Alveolus, proteinosis		12 (18%)	22 (33%)	43 (62%)
Pleura, fibrosis			1 (2%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
2-Year Study (continued)				
Respiratory System (continued)				
Nose	(55)	(66)	(66)	(67)
Inflammation, suppurative		2 (3%)	1 (2%)	
Olfactory epithelium, degeneration		4 (6%)	2 (3%)	1 (1%)
Olfactory epithelium, inflammation, suppurative		2 (3%)		
Respiratory epithelium, degeneration	2 (4%)	3 (5%)	4 (6%)	1 (1%)
Respiratory epithelium, inflammation, suppurative	6 (11%)	9 (14%)	9 (14%)	7 (10%)
Respiratory epithelium, metaplasia, squamous	2 (4%)	7 (11%)	8 (12%)	2 (3%)
Vomeronasal organ, inflammation, suppurative		1 (2%)		
Special Senses System				
Harderian gland		(1)	(2)	(3)
Hyperplasia				1 (33%)
Urinary System				
Kidney	(57)	(67)	(66)	(68)
Atrophy	1 (2%)			
Fibrosis		1 (1%)		
Inflammation, chronic		2 (3%)		1 (1%)
Inflammation, chronic active	1 (2%)	6 (9%)		1 (1%)
Inflammation, suppurative		1 (1%)	4 (6%)	6 (9%)
Mineralization	1 (2%)	1 (1%)		
Necrosis			1 (2%)	
Nephropathy	1 (2%)	1 (1%)	3 (5%)	1 (1%)
Bilateral, inflammation, suppurative	1 (2%)			
Bilateral, papilla, inflammation, suppurative	1 (2%)			
Bilateral, pelvis, dilatation	1 (2%)			
Cortex, cyst	1 (2%)	1 (1%)	2 (3%)	
Cortex, fibrosis	1 (2%)			
Cortex, inflammation, chronic			1 (2%)	
Pelvis, dilatation	9 (16%)	6 (9%)	9 (14%)	5 (7%)
Pelvis, hyperplasia, squamous				1 (1%)
Pelvis, inflammation, chronic			1 (2%)	
Pelvis, inflammation, chronic active		1 (1%)		1 (1%)
Pelvis, inflammation, suppurative	2 (4%)	1 (1%)		1 (1%)
Renal tubule, mineralization			2 (3%)	
Ureter			(2)	(4)
Concretion				2 (50%)
Inflammation, chronic active				1 (25%)
Inflammation, suppurative			1 (50%)	1 (25%)
Urethra	(2)	(4)	(5)	(12)
Calculus, microscopic observation only	1 (50%)	3 (75%)	4 (80%)	8 (67%)
Concretion	1 (50%)	1 (25%)	1 (20%)	4 (33%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m^3	1.25 mg/m^3	2.5 mg/m^3	5 mg/m^3
2-Year Study (continued)				
Urinary System (continued)				
Urinary bladder	(54)	(63)	(65)	(66)
Calculus, gross observation				1 (2%)
Calculus, microscopic observation only	1 (2%)	3 (5%)	3 (5%)	1 (2%)
Crystals		1 (2%)		
Hemorrhage		1 (2%)		
Inflammation		1 (2%)		
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic active	1 (2%)	2 (3%)	2 (3%)	1 (2%)
Inflammation, suppurative	2 (4%)	5 (8%)	2 (3%)	4 (6%)
Transitional epithelium, hyperplasia	1 (2%)			3 (5%)
Transitional epithelium, metaplasia, squamous	1 (2%)		1 (2%)	

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] No histopathologic examination was performed on these animals.
[c] This alteration is associated with injury to the parenchyma around the terminal bronchiole. It is listed as "alveolar epithelial hyperplasia" in the TDMS data tables for mice in this study.

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF NICKEL OXIDE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m^3	1.25 mg/m^3	2.5 mg/m^3	5 mg/m^3
Disposition Summary				
Animals initially in study	74	76	74	75
7-Month interim evaluation	5	5	5	5
15-Month interim evaluation	5	5	5	5
Early deaths				
Accidental deaths	1		1	
Moribund	15	18	9	16
Natural deaths	7	8	11	10
Survivors				
Terminal sacrifice	40	38	42	38
Died last week of study	1	2		
Pregnant/Missexed			1	1
Animals examined microscopically	74	76	73	74
Systems Examined At 7 Months With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
15-Month Interim Evaluation				
Alimentary System				
Liver	(5)	(5)	(5)	(5)
Hepatocellular adenoma		1 (20%)		
Respiratory System				
Lung	(5)	(5)	(5)	(5)
Alveolar/bronchiolar adenoma			1 (20%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Esophagus	(63)	(66)	(63)	(63)
Squamous cell carcinoma				1 (2%)
Gallbladder	(60)	(59)	(57)	(56)
Sarcoma, metastatic, mesentery				1 (2%)
Intestine large, colon	(60)	(61)	(58)	(57)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Intestine large, rectum	(55)	(50)	(43)	(43)
Intestine large, cecum	(60)	(60)	(57)	(56)
Leiomyosarcoma				1 (2%)
Sarcoma, metastatic, mesentery				1 (2%)
Intestine small, duodenum	(60)	(60)	(56)	(56)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Intestine small, jejunum	(59)	(59)	(56)	(56)
Intestine small, ileum	(58)	(57)	(56)	(54)
Liver	(64)	(66)	(63)	(63)
Hemangiosarcoma			1 (2%)	1 (2%)
Hemangiosarcoma, multiple		1 (2%)		
Hemangiosarcoma, metastatic, uterus		1 (2%)		
Hepatocellular carcinoma	7 (11%)	10 (15%)	8 (13%)	4 (6%)
Hepatocellular carcinoma, multiple	1 (2%)			
Hepatocellular adenoma	5 (8%)	7 (11%)	8 (13%)	5 (8%)
Hepatocellular adenoma, multiple			1 (2%)	
Hepatocellular adenoma, multiple, multiple	1 (2%)			
Hepatocholangiocarcinoma				1 (2%)
Histiocytic sarcoma	1 (2%)			2 (3%)
Sarcoma, metastatic, mesentery				1 (2%)
Mesentery	(2)	(2)	(1)	(3)
Hemangiosarcoma	1 (50%)			
Hepatocholangiocarcinoma, metastatic, liver				1 (33%)
Sarcoma				1 (33%)
Pancreas	(64)	(66)	(62)	(62)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Sarcoma, metastatic, mesentery				1 (2%)
Salivary glands	(64)	(66)	(63)	(63)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(64)	(63)	(62)	(60)
Sarcoma, metastatic, mesentery				1 (2%)
Squamous cell carcinoma	1 (2%)			
Squamous cell papilloma	1 (2%)			1 (2%)
Stomach, glandular	(63)	(63)	(62)	(60)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Sarcoma, metastatic, mesentery				1 (2%)
Tooth	(2)	(1)	(1)	(2)
Odontoma				1 (50%)
Cardiovascular System				
Heart	(64)	(66)	(63)	(64)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Endocrine System				
Adrenal cortex	(64)	(66)	(63)	(62)
Adenoma				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Adrenal medulla	(62)	(65)	(63)	(62)
Pheochromocytoma malignant	2 (3%)			
Pheochromocytoma benign	1 (2%)		1 (2%)	
Islets, pancreatic	(63)	(65)	(62)	(62)
Pituitary gland	(63)	(66)	(61)	(62)
Pars distalis, adenoma	6 (10%)	9 (14%)	8 (13%)	6 (10%)
Pars distalis, carcinoma	1 (2%)			1 (2%)
Pars intermedia, adenoma		1 (2%)	1 (2%)	1 (2%)
Thyroid gland	(62)	(66)	(63)	(64)
Bilateral, follicular cell, adenoma			1 (2%)	
Follicular cell, adenoma	2 (3%)	1 (2%)		1 (2%)
Follicular cell, carcinoma	1 (2%)			
General Body System				
Tissue NOS	(1)	(1)	(1)	(1)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (100%)		
Hemangiosarcoma, metastatic				1 (100%)
Fat, hemangiosarcoma			1 (100%)	
Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung	1 (100%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
2-Year Study (continued)				
Genital System				
Clitoral gland	(57)	(62)	(57)	(55)
Duct, adenoma		1 (2%)		
Ovary	(61)	(66)	(60)	(63)
Cystadenoma	1 (2%)		3 (5%)	
Granulosa-theca tumor benign			1 (2%)	
Sarcoma, metastatic, mesentery				1 (2%)
Teratoma benign	2 (3%)	1 (2%)		
Teratoma malignant				1 (2%)
Thecoma benign	1 (2%)			
Uterus	(64)	(66)	(62)	(63)
Carcinoma		1 (2%)		
Hemangioma			1 (2%)	
Hemangiosarcoma		2 (3%)	1 (2%)	1 (2%)
Histiocytic sarcoma	1 (2%)			
Leiomyoma	1 (2%)			
Polyp stromal	2 (3%)	4 (6%)		1 (2%)
Sarcoma, metastatic, mesentery				1 (2%)
Sarcoma stromal	1 (2%)		1 (2%)	
Teratoma malignant, metastatic				1 (2%)
Cervix, hemangiosarcoma		1 (2%)		
Hematopoietic System				
Bone marrow	(64)	(65)	(62)	(63)
Hemangiosarcoma			1 (2%)	
Hemangiosarcoma, metastatic				1 (2%)
Hemangiosarcoma, metastatic, spleen			1 (2%)	
Lymph node	(15)	(9)	(10)	(9)
Axillary, hemangiosarcoma	1 (7%)		1 (10%)	
Pancreatic, histiocytic sarcoma				1 (11%)
Pancreatic, sarcoma, metastatic, mesentery				1 (11%)
Renal, sarcoma, metastatic, mesentery				1 (11%)
Lymph node, bronchial	(54)	(63)	(59)	(62)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)	2 (3%)		
Histiocytic sarcoma				2 (3%)
Sarcoma, metastatic, mesentery				1 (2%)
Lymph node, mandibular	(61)	(63)	(59)	(58)
Sarcoma, metastatic, skin		1 (2%)		
Lymph node, mesenteric	(54)	(63)	(54)	(55)
Hemangioma				1 (2%)
Hemangiosarcoma, metastatic, liver			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Sarcoma, metastatic, mesentery				1 (2%)
Lymph node, mediastinal	(35)	(28)	(33)	(29)
Alveolar/bronchiolar carcinoma, metastatic		1 (4%)		
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (3%)	1 (4%)		
Hepatocholangiocarcinoma, metastatic, liver				1 (3%)
Histiocytic sarcoma				1 (3%)
Sarcoma, metastatic, mesentery				1 (3%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
2-Year Study (continued)				
Hematopoietic System (continued)				
Spleen	(64)	(66)	(63)	(63)
Hemangiosarcoma	2 (3%)	2 (3%)	5 (8%)	2 (3%)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma				2 (3%)
Sarcoma, metastatic, mesentery				1 (2%)
Thymus	(59)	(61)	(60)	(57)
Alveolar/bronchiolar carcinoma, metastatic		1 (2%)		
Alveolar/bronchiolar carcinoma, metastatic, lung	2 (3%)	1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma	1 (2%)			1 (2%)
Sarcoma, metastatic, mesentery				1 (2%)
Integumentary System				
Mammary gland	(63)	(66)	(63)	(63)
Adenoma		1 (2%)		
Carcinoma	2 (3%)	3 (5%)		3 (5%)
Skin	(4)	(8)	(6)	(12)
Hemangiosarcoma		1 (13%)		
Melanoma NOS		1 (13%)		
Sarcoma		1 (13%)	1 (17%)	1 (8%)
Squamous cell papilloma				1 (8%)
Pinna, sarcoma		1 (13%)		
Sebaceous gland, adenoma			1 (17%)	
Subcutaneous tissue, hemangiosarcoma	1 (25%)	1 (13%)		
Musculoskeletal System				
Bone	(64)	(65)	(63)	(63)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Skeletal muscle	(3)			(3)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (33%)			
Hepatocholangiocarcinoma, metastatic, liver				1 (33%)
Rhabdomyosarcoma	1 (33%)			
Sarcoma, metastatic, mesentery				1 (33%)
Nervous System				
Brain	(64)	(66)	(63)	(64)
Carcinoma, metastatic	1 (2%)			
Hypothalamus, carcinoma, metastatic				1 (2%)
Pons, carcinoma, metastatic				1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m^3	1.25 mg/m^3	2.5 mg/m^3	5 mg/m^3
2-Year Study (continued)				
Respiratory System				
Larynx	(62)	(63)	(62)	(63)
Lung	(64)	(66)	(63)	(64)
Alveolar/bronchiolar adenoma	2 (3%)	2 (3%)	10 (16%)	3 (5%)
Alveolar/bronchiolar adenoma, multiple		2 (3%)		
Alveolar/bronchiolar carcinoma	4 (6%)	10 (15%)	4 (6%)	5 (8%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		
Basosquamous tumor malignant, metastatic, ear	1 (2%)			
Hepatocellular carcinoma, metastatic		1 (2%)	1 (2%)	1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma				2 (3%)
Sarcoma, metastatic, mesentery				1 (2%)
Teratoma malignant, metastatic				1 (2%)
Special Senses System				
Ear	(2)	(1)	(1)	(1)
Basosquamous tumor malignant	1 (50%)			
Fibrosarcoma			1 (100%)	
External ear, fibrosarcoma	1 (50%)			
Harderian gland		(1)	(2)	(3)
Adenoma		1 (100%)	2 (100%)	3 (100%)
Urinary System				
Kidney	(64)	(66)	(63)	(63)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Teratoma malignant, metastatic				1 (2%)
Urinary bladder	(63)	(62)	(60)	(57)
Sarcoma, metastatic, mesentery				1 (2%)
Systemic Lesions				
Multiple organs[b]	(64)	(66)	(63)	(64)
Histiocytic sarcoma	2 (3%)			2 (3%)
Lymphoma malignant	13 (20%)	12 (18%)	9 (14%)	7 (11%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m^3	1.25 mg/m^3	2.5 mg/m^3	5 mg/m^3
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation		1	1	
2-Year study	37	49	45	40
Total primary neoplasms				
15-Month interim evaluation		1	1	
2-Year study	68	78	72	57
Total animals with benign neoplasms				
15-Month interim evaluation		1	1	
2-Year study	21	27	28	24
Total benign neoplasms				
15-Month interim evaluation		1	1	
2-Year study	25	30	38	25
Total animals with malignant neoplasms				
2-Year study	30	37	28	28
Total malignant neplasms				
2-Year study	43	47	34	32
Total animals with metastatic neoplasms				
2-Year study	5	6	3	6
Total metastatic neoplasms				
2-Year study	10	11	3	40
Total animals with uncertain neoplasms-benign or malignant				
2-Year study		1		
Total uncertain neoplasms				
2-Year study		1		

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³

Number of Days on Study	0 1 1	0 1 4	0 2 4	0 2 9	0 9 2	1 1 7	1 3 2	2 2 9	3 5 7	5 1 0	5 4 9	5 5 9	5 8 6	5 9 9	6 1 8	6 2 2	6 3 8	6 4 2	6 8 8	6 9 4	6 9 5	7 2 8	7 2 8	7 2 9	7 2 9
Carcass ID Number	1 2 0	0 9 5	1 3 2	1 0 6	1 0 8	0 8 6	1 0 5	0 8 7	1 1 0	0 8 1	1 5 4	1 1 4	1 2 8	0 8 3	1 3 4	1 4 4	0 9 0	1 0 9	1 3 8	1 3 7	1 3 0	0 9 6	1 1 3	0 8 9	0 9 9
Alimentary System																									
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	M	+	+	M	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+
Intestine small, ileum	+	+	A	M	+	+	+	+	+	+	+	+	M	+	A	+	+	+	+	+	+	+	M	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																				X					X
Hepatocellular carcinoma, multiple													X												
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple, multiple																									
Histiocytic sarcoma																									
Mesentery																								+	
Hemangiosarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																				X					
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	M	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant														X							X				
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Parathyroid gland	M	M	M	+	+	M	M	M	+	+	+	M	+	+	+	+	+	+	+	I	+	+	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pars distalis, adenoma																				X					
Pars distalis, carcinoma																									X
Thyroid gland	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
Follicular cell, carcinoma																									X

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2
Carcass ID Number	1 1 5	1 2 7	1 4 2	1 5 2	1 5 3	0 8 2	0 9 3	0 9 7	1 0 1	1 2 3	1 3 6	1 4 1	1 4 5	1 6 0	1 2 1	1 3 5	1 3 9	1 4 6	1 5 1	1 5 6	1 5 8	1 9 1	2 0 3	1 1 1	1 1 8
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	M	+	A	+	+	+	+	+	+	+	M	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma							X						X				X								
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma			X			X					X								X			X			
Hepatocellular adenoma, multiple, multiple		X																							
Histiocytic sarcoma																									
Mesentery																									
Hemangiosarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																			X						
Squamous cell papilloma					X																				
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+		+																						
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign					X																				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	I	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X			X											X										
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma					X																				
Follicular cell, carcinoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	1 1 9	1 2 9	1 3 0	1 3 1	1 4 7	1 0 2	1 1 2	1 2 4	1 2 6	1 5 0	1 0 4	1 1 6	1 4 9	1 5 9	Total Tissues/ Tumors
Alimentary System															
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Hepatocellular carcinoma		X					X								7
Hepatocellular carcinoma, multiple															1
Hepatocellular adenoma															5
Hepatocellular adenoma, multiple, multiple															1
Histiocytic sarcoma								X							1
Mesentery												+			2
Hemangiosarcoma												X			1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Squamous cell carcinoma															1
Squamous cell papilloma															1
Stomach, glandular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Tooth															2
Cardiovascular System															
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Alveolar/bronchiolar carcinoma, metastatic, lung															1
Endocrine System															
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Pheochromocytoma malignant															2
Pheochromocytoma benign															1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Pars distalis, adenoma		X										X			6
Pars distalis, carcinoma															1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Follicular cell, adenoma	X														2
Follicular cell, carcinoma															1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³
(continued)

Number of Days on Study	0 1 1	0 1 4	0 2 4	0 2 9	0 9 2	1 1 7	1 3 2	2 2 9	3 5 7	5 1 0	5 4 9	5 5 9	5 8 6	5 9 9	6 1 8	6 2 2	6 3 8	6 4 2	6 8 8	6 9 4	6 9 5	7 2 8	7 2 8	7 2 9	7 2 9
Carcass ID Number	1 2 0	0 9 5	1 3 2	1 0 6	1 0 8	0 8 6	1 0 5	0 8 7	1 1 0	0 8 1	1 5 4	1 1 4	1 2 8	0 8 3	1 3 4	1 4 4	0 9 0	1 0 9	1 3 8	1 3 7	1 0 0	0 9 6	1 1 3	0 8 9	0 9 9
General Body System																									
Tissue NOS																									
Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung																									
Genital System																									
Clitoral gland	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Teratoma benign					X	X																			
Thecoma benign																								X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leiomyoma																									
Polyp stromal												X													
Sarcoma stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node												+			+	+	+					+	+	+	
Axillary, hemangiosarcoma																							X		
Lymph node, bronchial	M	M	M	+	M	I	M	+	M	+	I	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Lymph node, mandibular	+	+	+	+		+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	M	+	M	A	M	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+
Lymph node, mediastinal	M	M	M	M	M	M	M	M	M	+	M	+	M	M	M	M	+	M	+	M	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X		
Thymus	+	+	+	+	M	+	M	+	+	+	+	+	+	+	I	+	+	+	+	+	M	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																				X					
Histiocytic sarcoma																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																				X					
Skin																+	+								
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																				+					
Alveolar/bronchiolar carcinoma, metastatic, lung																				X					
Rhabdomyosarcoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m^3
(continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	9	9	9	9	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	2	2	2	2
Carcass ID Number	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1
	1	2	4	5	5	8	9	9	0	2	3	4	4	6	2	3	3	4	5	5	5	9	0	1	1
	5	7	2	2	3	2	3	7	1	3	6	1	5	0	1	5	9	6	1	6	8	1	3	1	8
General Body System																									
Tissue NOS																									
Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	I	I	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	I	+
Cystadenoma										X															
Teratoma benign																									
Thecoma benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leiomyoma																									
Polyp stromal				X																					
Sarcoma stromal															X										
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+					+										+		+			
Axillary, hemangiosarcoma																									
Lymph node, bronchial	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	M	+	+	M	M	+	+	M	+	M	+	M	M	M	+	+	M	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Histiocytic sarcoma						X																			
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin										+															
Subcutaneous tissue, hemangiosarcoma										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+																		+					
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Rhabdomyosarcoma		X																							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	1 1 9	1 2 9	1 3 0	1 3 1	1 4 7	1 0 2	1 1 2	1 2 2	1 2 4	1 2 6	1 5 0	0 9 4	1 1 6	1 4 9	1 5 9	Total Tissues/ Tumors
General Body System																
Tissue NOS		+														1
Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung		X														1
Genital System																
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	57
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	61
Cystadenoma																1
Teratoma benign																2
Thecoma benign																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Histiocytic sarcoma								X								1
Leiomyoma	X															1
Polyp stromal																2
Sarcoma stromal																1
Hematopoietic System																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Lymph node							+		+				+	+		15
Axillary, hemangiosarcoma																1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Alveolar/bronchiolar carcinoma, metastatic, lung		X														1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	61
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	54
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	35
Alveolar/bronchiolar carcinoma, metastatic, lung		X														1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Hemangiosarcoma																2
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+		59
Alveolar/bronchiolar carcinoma, metastatic, lung		X														2
Histiocytic sarcoma																1
Integumentary System																
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Carcinoma															X	2
Skin							+									4
Subcutaneous tissue, hemangiosarcoma																1
Musculoskeletal System																
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Skeletal muscle																3
Alveolar/bronchiolar carcinoma, metastatic, lung																1
Rhabdomyosarcoma																1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³
(continued)

Number of Days on Study	0 1 1	0 1 4	0 2 4	0 2 9	0 9 2	1 1 7	1 3 2	2 2 9	3 5 7	5 1 0	5 4 9	5 5 9	5 8 6	5 9 9	6 1 8	6 2 2	6 3 8	6 4 2	6 8 8	6 9 4	6 9 5	7 2 8	7 2 8	7 2 9	7 2 9
Carcass ID Number	1 2 0	0 9 5	1 3 2	1 0 6	1 0 8	0 8 6	1 0 5	0 8 7	1 1 0	0 8 1	1 5 4	1 1 4	1 2 8	1 8 3	0 3 4	1 4 4	1 9 0	0 3 9	1 3 8	1 3 7	1 0 0	0 9 6	1 1 3	0 8 9	0 9 9
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic																									X
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Alveolar/bronchiolar carcinoma																				X					
Basosquamous tumor malignant, metastatic, ear																						X			
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																						+			
Basosquamous tumor malignant																						X			
External ear, fibrosarcoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant															X		X					X	X	X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³
(continued)

Number of Days on Study	729	729	729	729	729	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	732	732	732	732
Carcass ID Number	11515	12717	14222	15223	15533	08232	09933	09937	10101	12213	13316	14101	14505	16001	12015	13515	13959	14661	15116	15516	15858	09091	10313	11118	11518
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic																									
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma													X								X				
Basosquamous tumor malignant, metastatic, ear																									
Hepatocellular carcinoma, metastatic, liver							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear										+															
Basosquamous tumor malignant																									
External ear, fibrosarcoma										X															
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Lymphoma malignant	X				X						X									X		X	X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 0 mg/m³
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	1 1 9	1 2 9	1 3 0	1 3 1	1 4 7	1 0 2	1 1 2	1 2 4	1 2 6	1 5 0	0 9 4	1 1 6	1 4 9	1 5 9	Total Tissues/ Tumors
Nervous System															
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Carcinoma, metastatic															1
Respiratory System															
Larynx	+	M	+	+	+	+	+	+	+	+	+	+	+	+	62
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Alveolar/bronchiolar adenoma			X												2
Alveolar/bronchiolar carcinoma		X													4
Basosquamous tumor malignant, metastatic, ear															1
Hepatocellular carcinoma, metastatic, liver															1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Special Senses System															
Ear															2
Basosquamous tumor malignant															1
External ear, fibrosarcoma															1
Urinary System															
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Systemic Lesions															
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Histiocytic sarcoma								X							2
Lymphoma malignant							X					X			13

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³

	0	1	2	3	4	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7
Number of Days on Study	4	6	0	1	6	1	6	8	9	9	0	0	2	4	4	5	5	7	8	8	9	9	9	1	2
	6	2	3	7	9	0	6	3	3	7	3	9	6	0	4	2	7	6	3	3	0	2	5	1	0
	3	3	2	2	2	3	2	2	2	2	2	2	2	2	2	3	2	2	2	2	2	3	2	2	3
Carcass ID Number	0	2	9	9	5	1	4	9	6	4	8	5	8	7	7	0	6	7	7	9	8	0	5	9	1
	8	0	1	4	9	7	4	0	4	7	7	6	5	5	1	4	0	6	7	3	8	6	4	7	6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	A	+	+	A	+	A	+	+	+	+	+	A	A	+	+	+	+	+	M	+	+
Intestine large, colon	A	+	+	+	A	+	+	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+
Intestine large, cecum	A	+	+	+	A	+	+	A	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	A	+	+	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+
Intestine small, jejunum	A	+	+	+	A	+	+	A	+	A	+	+	+	+	+	A	A	+	+	+	+	+	A	+	+
Intestine small, ileum	A	+	+	+	A	+	+	A	+	A	+	+	+	+	+	A	A	+	+	+	+	+	A	M	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple														X											
Hemangiosarcoma, metastatic, uterus																									
Hepatocellular carcinoma					X										X			X				X		X	
Hepatocellular adenoma																									X
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X						X									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								X	
General Body System																									
Tissue NOS								+																	
Alveolar/bronchiolar carcinoma, metastatic, lung								X																	
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Duct, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Teratoma benign		X																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Hemangiosarcoma																	X								
Polyp stromal								X				X													
Cervix, hemangiosarcoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2
Carcass ID Number	2 8 6	2 5 1	2 5 3	2 5 8	2 7 2	2 7 9	3 1 3	2 4 9	2 6 6	2 6 9	2 7 3	2 8 2	2 8 9	2 9 8	3 1 2	2 4 5	2 4 6	2 5 0	2 6 1	2 7 8	2 8 0	2 9 2	3 1 1	2 4 1	2 6 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	M	M	+	+	M	+	M	+	+	+	+	M	M	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple																									
Hemangiosarcoma, metastatic, uterus																									
Hepatocellular carcinoma													X		X								X		
Hepatocellular adenoma					X	X	X						X												X
Mesentery				+																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth					+																				
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X										X					X							X	
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS																									
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Genital System																									
Clitoral gland	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Duct, adenoma			X																						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Teratoma benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Hemangiosarcoma																									
Polyp stromal											X														
Cervix, hemangiosarcoma																								X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	
Carcass ID Number	2 6 7	2 8 4	2 9 5	2 9 6	3 0 3	3 1 9	2 4 8	2 5 7	2 6 2	2 6 3	3 0 0	3 0 7	3 1 4	3 1 8	2 7 0	2 8 1	Total Tissues/ Tumors
Alimentary System																	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	61
Intestine large, rectum	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	M	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine small, ileum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	57
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Hemangiosarcoma, multiple																	1
Hemangiosarcoma, metastatic, uterus														X			1
Hepatocellular carcinoma			X							X							10
Hepatocellular adenoma					X												7
Mesentery										+							2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Tooth																	1
Cardiovascular System																	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Endocrine System																	
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	65
Parathyroid gland	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	55
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Pars distalis, adenoma		X								X			X				9
Pars intermedia, adenoma																X	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Follicular cell, adenoma																	1
General Body System																	
Tissue NOS																	1
Alveolar/bronchiolar carcinoma, metastatic, lung																	1
Genital System																	
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	62
Duct, adenoma																	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Teratoma benign																	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Carcinoma									X								1
Hemangiosarcoma														X			2
Polyp stromal							X										4
Cervix, hemangiosarcoma																	1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	0 4 6	1 6 2	2 0 3	3 1 7	4 6 9	5 1 0	5 6 6	5 8 3	5 9 3	5 9 7	6 0 3	6 0 9	6 2 6	6 4 0	6 4 4	6 5 2	6 5 7	6 7 6	6 8 3	6 8 3	6 9 0	6 9 2	6 9 5	7 1 1	7 2 0
Carcass ID Number	3 0 8	3 2 0	2 9 1	2 9 4	2 5 9	3 1 7	2 4 4	2 9 0	2 6 4	2 4 7	2 8 7	2 5 6	2 8 5	2 7 5	2 7 1	3 0 4	2 6 0	2 7 6	2 7 7	2 9 3	2 8 8	3 0 6	2 5 4	2 9 7	3 1 6
Hematopoietic System																									
Bone marrow	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node										+	+													+	
Lymph node, bronchial	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung								X														X			
Lymph node, mandibular	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin													X												
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	M	M	+	I	M	+	+	M	+	+	+	I	+	+	M	M	+	+	I	+	M	M	M	+
Alveolar/bronchiolar carcinoma, metastatic																					X				
Alveolar/bronchiolar carcinoma, metastatic, lung								X																	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	I	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic																					X				
Alveolar/bronchiolar carcinoma, metastatic, lung								X																	
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma																									
Skin				+			+		+				+	+											+
Hemangiosarcoma																									X
Melanoma NOS																									
Sarcoma									X																
Pinna, sarcoma													X												
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung								X																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord			+																						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	726	729	729	729	729	729	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	732	732
Carcass ID Number	28616	25513	25538	25582	27729	27793	31439	32466	32669	32733	32822	32899	33098	33412	32545	32560	32701	32818	32902	33091	33111	33142	33115	33265
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+		+						+							+			+		
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin																								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	M	M	M	+	I	+	M	+	+	M	M	M	+	I	+	+	+	M	M	M	M	M	+
Alveolar/bronchiolar carcinoma, metastatic																								
Alveolar/bronchiolar carcinoma, metastatic, lung																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X	
Thymus	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+
Alveolar/bronchiolar carcinoma, metastatic																								
Alveolar/bronchiolar carcinoma, metastatic, lung																								
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma			X																					X
Skin														+						+				
Hemangiosarcoma																								
Melanoma NOS																				X				
Sarcoma																								
Pinna, sarcoma																								
Subcutaneous tissue, hemangiosarcoma														X										
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																								
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	
Carcass ID Number	2 6 7	2 8 4	2 9 5	2 9 6	3 0 3	3 1 9	2 4 8	2 5 7	2 6 2	2 6 3	3 0 0	3 0 7	3 1 4	3 1 8	2 7 0	2 8 1	Total Tissues/ Tumors
Hematopoietic System																	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Lymph node								+									9
Lymph node, bronchial	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	63
Alveolar/bronchiolar carcinoma, metastatic, lung																	2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Sarcoma, metastatic, skin																	1
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	63
Lymph node, mediastinal	+	I	M	M	I	+	M	+	+	+	+	I	M	M	M	I	28
Alveolar/bronchiolar carcinoma, metastatic																	1
Alveolar/bronchiolar carcinoma, metastatic, lung																	1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Hemangiosarcoma																	2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	61
Alveolar/bronchiolar carcinoma, metastatic																	1
Alveolar/bronchiolar carcinoma, metastatic, lung																	1
Integumentary System																	
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Adenoma																	1
Carcinoma										X							3
Skin																	8
Hemangiosarcoma																	1
Melanoma NOS																	1
Sarcoma																	1
Pinna, sarcoma																	1
Subcutaneous tissue, hemangiosarcoma																	1
Musculoskeletal System																	
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Alveolar/bronchiolar carcinoma, metastatic, lung																	1
Nervous System																	
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Spinal cord																	1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	0 4 6	1 6 2	2 0 3	3 1 7	4 6 9	5 1 0	5 6 6	5 8 3	5 9 3	5 9 7	6 0 3	6 0 9	6 2 6	6 4 0	6 4 4	6 5 2	6 5 7	6 7 6	6 8 3	6 8 3	6 9 0	6 9 2	6 9 5	7 1 1	7 2 0
Carcass ID Number	3 0 8	3 2 0	2 9 1	2 9 4	2 5 9	3 1 7	2 4 4	2 9 0	2 6 4	2 4 7	2 8 7	2 5 6	2 8 5	2 7 5	2 7 1	3 0 4	2 6 0	2 7 6	2 7 3	2 9 3	2 8 8	3 0 6	2 5 4	2 9 7	3 1 6
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma								X										X			X	X	X		
Alveolar/bronchiolar carcinoma, multiple																	X								
Hepatocellular carcinoma, metastatic															X										
Nose	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Harderian gland												+													
Adenoma												X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant										X	X								X				X	X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	726	729	729	729	729	729	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	732	732
Carcass ID Number	28616	25611	25613	25618	27612	27619	31613	34619	36616	36619	37613	38612	38619	39618	31612	34615	34616	35610	36611	37618	38610	39612	31611	34611	36615
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	I	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X														
Alveolar/bronchiolar adenoma, multiple									X																
Alveolar/bronchiolar carcinoma							X											X			X				X
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant	X					X				X		X							X				X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 1.25 mg/m³
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	
Carcass ID Number	2 6 7	2 8 4	2 9 5	2 9 6	3 0 3	3 1 9	2 4 8	2 5 7	2 6 2	2 6 3	3 0 0	3 0 7	3 1 4	3 1 8	2 7 0	2 8 1	Total Tissues/ Tumors
Respiratory System																	
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	63
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Alveolar/bronchiolar adenoma																	2
Alveolar/bronchiolar adenoma, multiple									X								2
Alveolar/bronchiolar carcinoma													X				10
Alveolar/bronchiolar carcinoma, multiple																	1
Hepatocellular carcinoma, metastatic																	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	65
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Special Senses System																	
Ear															+		1
Harderian gland																	1
Adenoma																	1
Urinary System																	
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Systemic Lesions																	
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	66
Lymphoma malignant		X															12

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³

Number of Days on Study	0 1 6	0 1 9	0 3 6	0 5 8	3 1 5	3 2 1	3 2 6	4 5 1	5 3 8	5 6 6	5 7 0	5 8 4	5 8 7	6 3 0	6 4 0	6 5 9	6 6 9	6 7 0	6 7 0	6 7 6	6 8 1	7 2 9	7 2 9	7 2 9
Carcass ID Number	4 3 7	4 2 3	4 1 0	4 5 2	4 0 9	4 2 0	4 2 1	4 0 7	4 1 5	4 1 4	4 1 3	4 1 6	4 1 9	4 5 5	4 1 2	4 6 6	4 7 0	4 2 7	4 3 3	4 4 9	4 3 4	4 4 1	4 4 8	4 4 2
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	A	A	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	A	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	M	+	+
Intestine large, cecum	A	+	A	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+
Intestine small, duodenum	A	A	A	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+
Intestine small, jejunum	A	A	A	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+
Intestine small, ileum	A	A	A	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X	
Hepatocellular carcinoma								X		X	X								X					
Hepatocellular adenoma															X		X			X				X
Hepatocellular adenoma, multiple																								
Mesentery																					+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Tooth																								
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	M	M	M	M	M	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma															X									
Pars intermedia, adenoma																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, follicular cell, adenoma																								
General Body System																								
Tissue NOS																								
Fat, hemangiosarcoma																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	I	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+
Cystadenoma																								
Granulosa-theca tumor benign																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Hemangioma													X											
Hemangiosarcoma																					X			
Sarcoma stromal																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	43 0	43 2	44 1	44 2	44 6	45 8	46 1	48 0	42 6	44 0	44 3	44 7	45 0	55 9	57 2	70 2	44 4	45 3	55 6	50 7	40 5	51 7	43 8	44 8	46 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	M	+	+	+	+	M	M	+	+	+	+	M	M	M	+	+	M	M	+	+	+	+	M	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma	X	X										X													
Hepatocellular adenoma									X													X			
Hepatocellular adenoma, multiple																									
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth							+																		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																							X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X												X			X						
Pars intermedia, adenoma																								X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, follicular cell, adenoma																									
General Body System																									
Tissue NOS																									
Fat, hemangiosarcoma																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma			X										X										X		
Granulosa-theca tumor benign	X																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																									
Sarcoma stromal																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 0 3	4 0 8	4 2 8	4 2 9	4 3 1	4 3 5	4 6 9	4 7 3	4 7 8	4 0 4	4 2 4	4 2 5	4 6 0	4 6 3		Total Tissues/ Tumors
Alimentary System																
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+		57
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+		58
Intestine large, rectum	+	+	M	+	M	+	+	M	M	+	M	M	+	+		43
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+		57
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+		56
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+		56
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+		56
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Hemangiosarcoma																1
Hepatocellular carcinoma								X								8
Hepatocellular adenoma					X					X						8
Hepatocellular adenoma, multiple						X										1
Mesentery																1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+		62
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+		62
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+		62
Tooth																1
Cardiovascular System																
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Endocrine System																
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Pheochromocytoma benign																1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+		62
Parathyroid gland	+	+	M	+	+	M	+	+	+	M	M	+	+	+		48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+		61
Pars distalis, adenoma					X	X			X			X				8
Pars intermedia, adenoma																1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Bilateral, follicular cell, adenoma						X										1
General Body System																
Tissue NOS						+										1
Fat, hemangiosarcoma						X										1
Genital System																
Clitoral gland	+	+	I	M	+	+	+	+	+	+	+	+	+	+		57
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+		60
Cystadenoma																3
Granulosa-theca tumor benign																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+		62
Hemangioma																1
Hemangiosarcoma																1
Sarcoma stromal											X					1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	0 1 6	0 1 9	0 3 6	0 5 8	3 1 5	3 2 1	3 2 6	4 5 1	5 3 8	5 6 6	5 7 0	5 8 4	5 8 7	6 3 0	6 4 0	6 5 9	6 6 9	6 7 0	6 7 0	6 7 6	6 8 1	7 2 9	7 2 9	7 2 9
Carcass ID Number	4 3 7	4 2 3	4 1 0	4 5 2	4 0 9	4 2 0	4 2 1	4 0 7	4 1 5	4 1 4	4 1 3	4 1 6	4 1 9	4 5 5	4 1 2	4 6 6	4 7 0	4 2 7	4 3 3	4 4 9	4 3 4	4 0 1	4 1 8	4 2 2
Hematopoietic System																								
Bone marrow	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X								
Hemangiosarcoma, metastatic, spleen									X															
Lymph node								+											+	+		+		+
Axillary, hemangiosarcoma																								
Lymph node, bronchial	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	A	M	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	M	M	+	+	M	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver																							X	
Lymph node, mediastinal	M	M	M	M	M	+	+	+	+	+	+	M	I	+	+	+	M	+	M	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X							X								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin							+											+		+	+			
Sarcoma																								
Sebaceous gland, adenoma																		X						
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X		X	X				X			
Alveolar/bronchiolar carcinoma														X										
Hepatocellular carcinoma, metastatic								X																
Nose	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear												+												
Fibrosarcoma												X												
Harderian gland															+									
Adenoma															X									
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant						X	X											X			X			X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	731	731	731	731	731	732	732	732	732	732
Carcass ID Number	43026	43028	43041	43042	43046	43058	43061	43080	43026	43040	43043	43047	43050	43059	43072	43022	43044	43053	43056	43057	43015	43017	43038	43048	43068
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, spleen																									
Lymph node									+									+	+		+				
Axillary, hemangiosarcoma									X																
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver																									
Lymph node, mediastinal	+	M	M	+	M	+	+	M	M	M	M	M	M	M	+	M	M	+	M	M	+	M	M	I	I
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X									X							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin																									
Sarcoma																									
Sebaceous gland, adenoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X							X						X			X		X			
Alveolar/bronchiolar carcinoma											X														
Hepatocellular carcinoma, metastatic																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Fibrosarcoma																									
Harderian gland	+																								
Adenoma	X																								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																		X			X				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 2.5 mg/m³
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 0 0 3	4 0 8	4 0 8	4 2 9	4 3 1	4 3 5	4 4 6 9	4 4 7 3	4 4 7 8	4 4 0 4	4 4 2 4	4 4 2 5	4 4 6 0	4 4 6 3		Total Tissues/ Tumors
Hematopoietic System																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+		62
Hemangiosarcoma																1
Hemangiosarcoma, metastatic, spleen																1
Lymph node				+												10
Axillary, hemangiosarcoma																1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+		59
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+		59
Lymph node, mesenteric	+	M	M	+	+	+	+	+	M	+	+	+	+	+		54
Hemangiosarcoma, metastatic, liver																1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	M	I	+	+	M	+		33
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Hemangiosarcoma										X						5
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+		60
Integumentary System																
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Skin											+			+		6
Sarcoma											X					1
Sebaceous gland, adenoma																1
Musculoskeletal System																
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Nervous System																
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Respiratory System																
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+		62
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Alveolar/bronchiolar adenoma								X								10
Alveolar/bronchiolar carcinoma		X	X													4
Hepatocellular carcinoma, metastatic																1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+		62
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Special Senses System																
Ear																1
Fibrosarcoma																1
Harderian gland																2
Adenoma																2
Urinary System																
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+		60
Systemic Lesions																
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+		63
Lymphoma malignant			X	X												9

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³

Number of Days on Study	0 7 0	1 4 1	2 9 3	4 2 6	4 6 9	4 9 5	4 9 8	5 1 0	5 3 3	5 8 4	5 9 5	6 0 2	6 1 9	6 4 0	6 4 4	6 4 4	6 5 8	6 7 0	6 7 3	6 7 5	6 8 4	6 9 6	6 9 9	7 1 3
Carcass ID Number	5 9 9	6 0 5	5 8 5	5 8 4	5 9 5	6 3 6	6 2 0	6 1 1	6 3 2	6 2 6	5 6 8	5 6 3	5 6 6	6 1 1	6 3 1	5 9 1	5 9 3	6 2 1	6 0 2	6 9 4	6 0 6	6 2 4	6 1 7	5 6 9	5 7 2
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																								
Gallbladder	+	A	+	+	+	M	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Sarcoma, metastatic, mesentery																			X					
Intestine large, colon	+	A	+	+	+	A	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver													X											
Intestine large, rectum	+	A	+	+	+	A	A	A	A	A	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	A	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Leiomyosarcoma																							X	
Sarcoma, metastatic, mesentery																			X					
Intestine small, duodenum	+	A	+	+	+	A	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Hepatocholangiocarcinoma, metastatic, liver													X											
Intestine small, jejunum	+	A	+	+	+	A	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Intestine small, ileum	+	A	+	+	+	A	A	A	A	A	+	+	+	A	+	+	+	+	M	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X										
Hepatocellular carcinoma															X				X					
Hepatocellular adenoma																								
Hepatocholangiocarcinoma													X											
Histiocytic sarcoma						X				X														
Sarcoma, metastatic, mesentery																			X					
Mesentery							+						+						+					
Hepatocholangiocarcinoma, metastatic, liver													X											
Sarcoma																			X					
Pancreas	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver													X											
Sarcoma, metastatic, mesentery																			X					
Salivary glands	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery																			X					
Squamous cell papilloma																						X		
Stomach, glandular	+	A	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver													X											
Sarcoma, metastatic, mesentery																			X					
Tooth																			+					
Odontoma																								
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver													X											
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Adenoma																								
Hepatocholangiocarcinoma, metastatic, liver													X											
Adrenal medulla	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³
(continued)

Number of Days on Study	7 2 0	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	5 7 8	6 1 0	5 6 4	5 9 2	6 1 2	6 3 0	6 3 8	6 4 0	5 6 2	5 8 8	5 8 9	6 2 2	6 2 7	6 2 8	5 6 6	5 6 7	5 7 0	5 7 3	5 7 4	5 7 9	5 8 3	5 9 6	6 0 3	6 0 9	6 1 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma											X														
Gallbladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery																									
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Intestine large, rectum	A	+	+	+	M	+	+	M	M	M	M	+	+	+	+	+	+	+	+	M	+	+	M	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Sarcoma, metastatic, mesentery																									
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma																									
Hepatocellular adenoma	X	X	X			X						X													
Hepatocholangiocarcinoma																									
Histiocytic sarcoma																									
Sarcoma, metastatic, mesentery																									
Mesentery																									
Hepatocholangiocarcinoma, metastatic, liver																									
Sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Sarcoma, metastatic, mesentery																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery																									
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Sarcoma, metastatic, mesentery																									
Tooth											+														
Odontoma											X														
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Hepatocholangiocarcinoma, metastatic, liver																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	I	+	+	+	M	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	
Carcass ID Number	5 6 5	5 7 7	5 8 2	6 0 0	6 1 3	6 3 4	6 3 9	5 6 1	5 8 6	5 9 0	6 2 5	6 3 7	5 8 1	5 8 7	6 3 5	Total Tissues/ Tumors
Alimentary System																
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Squamous cell carcinoma																1
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	56
Sarcoma, metastatic, mesentery																1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	57
Hepatocholangiocarcinoma, metastatic, liver																1
Intestine large, rectum	+	+	+	+	M	+	M	+	M	M	+	+	+	+	M	43
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	56
Leiomyosarcoma																1
Sarcoma, metastatic, mesentery																1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	56
Hepatocholangiocarcinoma, metastatic, liver																1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	56
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Hemangiosarcoma																1
Hepatocellular carcinoma	X													X		4
Hepatocellular adenoma																5
Hepatocholangiocarcinoma																1
Histiocytic sarcoma																2
Sarcoma, metastatic, mesentery																1
Mesentery																3
Hepatocholangiocarcinoma, metastatic, liver																1
Sarcoma																1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Hepatocholangiocarcinoma, metastatic, liver																1
Sarcoma, metastatic, mesentery																1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Sarcoma, metastatic, mesentery																1
Squamous cell papilloma																1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Hepatocholangiocarcinoma, metastatic, liver																1
Sarcoma, metastatic, mesentery																1
Tooth																2
Odontoma																1
Cardiovascular System																
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Hepatocholangiocarcinoma, metastatic, liver																1
Endocrine System																
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Adenoma					X											1
Hepatocholangiocarcinoma, metastatic, liver																1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³
(continued)

Number of Days on Study	0 7 0	1 4 1	2 9 3	4 2 6	4 6 9	4 9 5	4 9 8	5 1 0	5 3 3	5 8 4	5 9 5	6 0 2	6 1 9	6 4 0	6 4 4	6 4 4	6 5 8	6 7 0	6 7 3	6 7 5	6 8 4	6 9 6	6 9 9	7 1 3
Carcass ID Number	5 9 9	6 0 5	5 8 5	5 8 4	5 9 5	6 3 6	6 2 0	6 1 1	6 3 2	6 2 6	5 6 8	5 6 3	6 1 6	6 3 1	6 9 1	6 9 3	6 2 1	6 0 2	6 9 4	6 0 6	6 2 4	6 1 7	6 6 9	5 7 2
Endocrine System (continued)																								
Pituitary gland	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pars distalis, adenoma																			X				X	
Pars distalis, carcinoma																				X				
Pars intermedia, adenoma																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																	X							
General Body System																								
Tissue NOS																						+		
Hemangiosarcoma, metastatic																						X		
Genital System																								
Clitoral gland	M	M	M	+	+	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery																			X					
Teratoma malignant								X																
Uterus	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Polyp stromal																								
Sarcoma, metastatic, mesentery																			X					
Teratoma malignant, metastatic								X																
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic																						X		
Lymph node				+						+	+	+							+					
Pancreatic, histiocytic sarcoma										X														
Pancreatic, sarcoma, metastatic, mesentery																			X					
Renal, sarcoma, metastatic, mesentery																			X					
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X				X														
Sarcoma, metastatic, mesentery																			X					
Lymph node, mandibular	+	+	+	+	+	M	+	+	A	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	M	+	+	+	M	+	M	M	M	+	+	+	+	+	+	+	M	+	M	+	M	+	+
Hemangioma																								
Hepatocholangiocarcinoma, metastatic, liver													X											
Sarcoma, metastatic, mesentery																			X					
Lymph node, mediastinal	M	M	M	+	+	+	+	M	M	M	+	+	+	M	+	+	+	+	+	M	M	+	+	M
Hepatocholangiocarcinoma, metastatic, liver													X											
Histiocytic sarcoma						X																		
Sarcoma, metastatic, mesentery																			X					
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																	X					X		
Hepatocholangiocarcinoma, metastatic, liver													X											
Histiocytic sarcoma						X				X														
Sarcoma, metastatic, mesentery																			X					
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Hepatocholangiocarcinoma, metastatic, liver													X											
Histiocytic sarcoma						X																		
Sarcoma, metastatic, mesentery																			X					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³
(continued)

Number of Days on Study	7 2 0	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	5 7 8	6 1 0	5 6 4	5 9 2	6 1 2	6 3 0	6 3 8	6 4 0	5 6 2	5 8 8	5 8 9	6 2 2	6 2 7	6 2 8	5 6 6	5 6 7	5 7 0	5 7 3	5 7 4	5 7 9	5 8 3	5 9 6	6 0 3	6 0 9	6 1 9
Endocrine System (continued)																								
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X															
Pars distalis, carcinoma																								
Pars intermedia, adenoma					X																			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								
General Body System																								
Tissue NOS																								
Hemangiosarcoma, metastatic																								
Genital System																								
Clitoral gland	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery																								
Teratoma malignant																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Polyp stromal									X															
Sarcoma, metastatic, mesentery																								
Teratoma malignant, metastatic																								
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic																								
Lymph node																+								
Pancreatic, histiocytic sarcoma																								
Pancreatic, sarcoma, metastatic, mesentery																								
Renal, sarcoma, metastatic, mesentery																								
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Histiocytic sarcoma																								
Sarcoma, metastatic, mesentery																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Hemangioma																								X
Hepatocholangiocarcinoma, metastatic, liver																								
Sarcoma, metastatic, mesentery																								
Lymph node, mediastinal	+	M	+	M	+	M	+	M	I	+	I	M	M	M	+	I	M	+	M	M	I	+	M	I	M
Hepatocholangiocarcinoma, metastatic, liver																								
Histiocytic sarcoma																								
Sarcoma, metastatic, mesentery																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Hepatocholangiocarcinoma, metastatic, liver																								
Histiocytic sarcoma																								
Sarcoma, metastatic, mesentery																								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	M	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																								
Histiocytic sarcoma																								
Sarcoma, metastatic, mesentery																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	
Carcass ID Number	5 6 5	5 7 7	5 8 2	6 0 0	6 1 3	6 3 4	6 3 9	5 6 1	5 8 6	5 9 0	6 2 5	6 3 7	6 8 1	6 8 7	6 3 5	Total Tissues/ Tumors
Endocrine System (continued)																
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Pars distalis, adenoma	X					X				X						6
Pars distalis, carcinoma			·													1
Pars intermedia, adenoma																1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Follicular cell, adenoma																1
General Body System																
Tissue NOS																1
Hemangiosarcoma, metastatic																1
Genital System																
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Sarcoma, metastatic, mesentery																1
Teratoma malignant																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Hemangiosarcoma												X				1
Polyp stromal																1
Sarcoma, metastatic, mesentery																1
Teratoma malignant, metastatic																1
Hematopoietic System																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Hemangiosarcoma, metastatic																1
Lymph node	+					+									+	9
Pancreatic, histiocytic sarcoma																1
Pancreatic, sarcoma, metastatic, mesentery																1
Renal, sarcoma, metastatic, mesentery																1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Histiocytic sarcoma																2
Sarcoma, metastatic, mesentery																1
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Hemangioma																1
Hepatocholangiocarcinoma, metastatic, liver																1
Sarcoma, metastatic, mesentery																1
Lymph node, mediastinal	M	+	+	M	M	+	M	+	M	+	+	M	M	M	+	29
Hepatocholangiocarcinoma, metastatic, liver																1
Histiocytic sarcoma																1
Sarcoma, metastatic, mesentery																1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Hemangiosarcoma																2
Hepatocholangiocarcinoma, metastatic, liver																1
Histiocytic sarcoma																2
Sarcoma, metastatic, mesentery																1
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	57
Hepatocholangiocarcinoma, metastatic, liver																1
Histiocytic sarcoma																1
Sarcoma, metastatic, mesentery																1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³
(continued)

Number of Days on Study	0 7 0	1 4 1	2 9 3	4 2 6	4 6 9	4 9 5	4 9 8	5 1 0	5 3 3	5 8 4	5 9 5	5 0 2	6 6 9	6 1 0	6 4 4	6 4 4	6 5 8	6 7 0	6 7 3	6 7 5	6 8 4	6 9 6	6 9 9	7 1 3
Carcass ID Number	5 9 9	6 0 5	5 8 5	5 8 4	5 9 5	6 3 6	6 2 0	6 1 1	6 3 2	6 2 6	5 6 8	5 6 3	6 1 6	6 3 1	5 9 1	5 9 3	6 2 1	6 0 2	5 9 4	6 0 6	6 2 4	6 1 7	6 6 9	5 7 2
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																							X	
Skin	+		+				+	+		+											+			+
Sarcoma																								
Squamous cell papilloma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle													+						+					
Hepatocholangiocarcinoma, metastatic, liver													X											
Sarcoma, metastatic, mesentery																			X					
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hypothalamus, carcinoma, metastatic																				X				
Pons, carcinoma, metastatic																				X				
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X											
Alveolar/bronchiolar carcinoma					X												X					X		
Hepatocellular carcinoma, metastatic																X								
Hepatocholangiocarcinoma, metastatic, liver													X											
Histiocytic sarcoma						X				X														
Sarcoma, metastatic, mesentery																			X					
Teratoma malignant, metastatic								X																
Nose	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear																								
Eye																								
Harderian gland																								
Adenoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver													X											
Teratoma malignant, metastatic								X																
Urethra							+																	
Urinary bladder	+	A	+	+	+	A	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery																			X					
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X				X														
Lymphoma malignant				X							X													

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³
(continued)

Number of Days on Study	7 2 0	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	5 7 8	6 1 0	5 6 4	5 9 2	6 1 2	6 3 0	6 3 8	6 4 0	5 6 2	5 8 8	5 8 9	6 2 2	6 2 7	6 2 8	5 6 6	5 6 7	5 7 0	5 7 3	5 7 4	5 7 9	5 8 3	5 9 6	6 0 3	6 0 9	6 1 9
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma		X																X							
Skin	+																							+	
Sarcoma																									
Squamous cell papilloma																								X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Hepatocholangiocarcinoma, metastatic, liver																									
Sarcoma, metastatic, mesentery																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hypothalamus, carcinoma, metastatic																									
Pons, carcinoma, metastatic																									
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X													X				
Alveolar/bronchiolar carcinoma										X															
Hepatocellular carcinoma, metastatic																									
Hepatocholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Sarcoma, metastatic, mesentery																									
Teratoma malignant, metastatic																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																				+					+
Harderian gland																	+			+					
Adenoma																	X			X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Teratoma malignant, metastatic																									
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant	X																	X		X					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nickel Oxide: 5 mg/m³
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	
Carcass ID Number	5 6 5	5 7 7	5 8 2	6 0 0	6 1 3	6 3 4	6 3 9	5 6 1	5 8 6	5 9 0	6 2 5	6 3 7	5 8 1	5 8 7	6 3 5	Total Tissues/ Tumors
Integumentary System																
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Carcinoma																3
Skin													+	+	+	12
Sarcoma													X			1
Squamous cell papilloma																1
Musculoskeletal System																
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Skeletal muscle																3
Hepatocholangiocarcinoma, metastatic, liver																1
Sarcoma, metastatic, mesentery																1
Nervous System																
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Hypothalamus, carcinoma, metastatic																1
Pons, carcinoma, metastatic																1
Respiratory System																
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Alveolar/bronchiolar adenoma																3
Alveolar/bronchiolar carcinoma			X													5
Hepatocellular carcinoma, metastatic																1
Hepatocholangiocarcinoma, metastatic, liver																1
Histiocytic sarcoma																2
Sarcoma, metastatic, mesentery																1
Teratoma malignant, metastatic																1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	62
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Special Senses System																
Ear															+	1
Eye																2
Harderian gland												+				3
Adenoma												X				3
Urinary System																
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	63
Hepatocholangiocarcinoma, metastatic, liver																1
Teratoma malignant, metastatic																1
Urethra																1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+		+	57
Sarcoma, metastatic, mesentery																1
Systemic Lesions																
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	64
Histiocytic sarcoma																2
Lymphoma malignant		X				X										7

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Oxide

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate[a]	3/62 (5%)	0/65 (0%)	1/63 (2%)	0/62 (0%)
Adjusted rate[b]	6.5%	0.0%	2.4%	0.0%
Terminal rate[c]	1/41 (2%)	0/39 (0%)	1/42 (2%)	0/38 (0%)
First incidence (days)	599	—[e]	729 (T)	—
Life table test[d]	P=0.094N	P=0.121N	P=0.310N	P=0.128N
Logistic regression test[d]	P=0.089N	P=0.110N	P=0.301N	P=0.118N
Cochran-Armitage test[d]	P=0.090N			
Fisher exact test[d]		P=0.113N	P=0.303N	P=0.122N
Harderian Gland: Adenoma				
Overall rate	0/64 (0%)	1/66 (2%)	2/63 (3%)	3/64 (5%)
Adjusted rate	0.0%	1.8%	4.4%	7.9%
Terminal rate	0/41 (0%)	0/40 (0%)	1/42 (2%)	3/38 (8%)
First incidence (days)	—	609	640	729 (T)
Life table test	P=0.058	P=0.519	P=0.247	P=0.108
Logistic regression test	P=0.063	P=0.496	P=0.239	P=0.108
Cochran-Armitage test	P=0.061			
Fisher exact test		P=0.508	P=0.244	P=0.122
Liver: Hepatocellular Adenoma				
Overall rate	6/64 (9%)	7/66 (11%)	9/63 (14%)	5/63 (8%)
Adjusted rate	14.6%	17.0%	19.7%	12.5%
Terminal rate	6/41 (15%)	6/40 (15%)	6/42 (14%)	3/38 (8%)
First incidence (days)	729 (T)	720	640	720
Life table test	P=0.479N	P=0.481	P=0.307	P=0.554N
Logistic regression test	P=0.448N	P=0.485	P=0.288	P=0.542N
Cochran-Armitage test	P=0.455N			
Fisher exact test		P=0.524	P=0.281	P=0.511N
Liver: Hepatocellular Carcinoma				
Overall rate	8/64 (13%)	10/66 (15%)	8/63 (13%)	4/63 (6%)
Adjusted rate	18.1%	21.0%	16.3%	9.2%
Terminal rate	6/41 (15%)	5/40 (13%)	4/42 (10%)	2/38 (5%)
First incidence (days)	586	469	451	644
Life table test	P=0.126N	P=0.409	P=0.591N	P=0.208N
Logistic regression test	P=0.103N	P=0.475	P=0.604N	P=0.164N
Cochran-Armitage test	P=0.115N			
Fisher exact test		P=0.428	P=0.592	P=0.190N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	14/64 (22%)	16/66 (24%)	17/63 (27%)	9/63 (14%)
Adjusted rate	32.2%	33.9%	34.0%	20.9%
Terminal rate	12/41 (29%)	10/40 (25%)	10/42 (24%)	5/38 (13%)
First incidence (days)	586	469	451	644
Life table test	P=0.172N	P=0.413	P=0.365	P=0.227N
Logistic regression test	P=0.122N	P=0.525	P=0.345	P=0.159N
Cochran-Armitage test	P=0.149N			
Fisher exact test		P=0.456	P=0.322	P=0.190N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/64 (3%)	4/66 (6%)	10/63 (16%)	3/64 (5%)
Adjusted rate	4.7%	9.3%	21.4%	7.1%
Terminal rate	1/41 (2%)	3/40 (8%)	6/42 (14%)	2/38 (5%)
First incidence (days)	728	652	630	619
Life table test	P=0.359	P=0.334	P=0.021	P=0.474
Logistic regression test	P=0.394	P=0.369	P=0.017	P=0.517
Cochran-Armitage test	P=0.379			
Fisher exact test		P=0.355	P=0.014	P=0.500
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	4/64 (6%)	11/66 (17%)	4/63 (6%)	5/64 (8%)
Adjusted rate	9.4%	22.8%	9.0%	10.8%
Terminal rate	3/41 (7%)	5/40 (13%)	3/42 (7%)	2/38 (5%)
First incidence (days)	694	583	630	469
Life table test	P=0.407N	P=0.057	P=0.633N	P=0.483
Logistic regression test	P=0.364N	P=0.069	P=0.642N	P=0.525
Cochran-Armitage test	P=0.385N			
Fisher exact test		P=0.055	P=0.632	P=0.500
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	6/64 (9%)	15/66 (23%)	12/63 (19%)	8/64 (13%)
Adjusted rate	13.8%	30.8%	25.7%	17.4%
Terminal rate	4/41 (10%)	8/40 (20%)	8/42 (19%)	4/38 (11%)
First incidence (days)	694	583	630	469
Life table test	P=0.542	P=0.034	P=0.114	P=0.363
Logistic regression test	P=0.487N	P=0.043	P=0.099	P=0.422
Cochran-Armitage test	P=0.516N			
Fisher exact test		P=0.033	P=0.095	P=0.389
Mammary Gland: Carcinoma				
Overall rate	2/64 (3%)	3/66 (5%)	0/63 (0%)	3/64 (5%)
Adjusted rate	4.6%	7.5%	0.0%	7.4%
Terminal rate	1/41 (2%)	3/40 (8%)	0/42 (0%)	1/38 (3%)
First incidence (days)	694	729 (T)	—	699
Life table test	P=0.478	P=0.489	P=0.245N	P=0.472
Logistic regression test	P=0.495	P=0.521	P=0.237N	P=0.509
Cochran-Armitage test	P=0.498			
Fisher exact test		P=0.515	P=0.252N	P=0.500
Mammary Gland: Adenoma or Carcinoma				
Overall rate	2/64 (3%)	4/66 (6%)	0/63 (0%)	3/64 (5%)
Adjusted rate	4.6%	9.4%	0.0%	7.4%
Terminal rate	1/41 (2%)	3/40 (8%)	0/42 (0%)	1/38 (3%)
First incidence (days)	694	683	—	699
Life table test	P=0.547	P=0.334	P=0.245N	P=0.472
Logistic regression test	P=0.571	P=0.370	P=0.237N	P=0.509
Cochran-Armitage test	P=0.569			
Fisher exact test		P=0.355	P=0.252N	P=0.500

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
Ovary: Cystadenoma				
Overall rate	1/61 (2%)	0/66 (0%)	3/60 (5%)	0/63 (0%)
Adjusted rate	2.6%	0.0%	7.1%	0.0%
Terminal rate	1/38 (3%)	0/40 (0%)	3/42 (7%)	0/38 (0%)
First incidence (days)	729 (T)	—	729 (T)	—
Life table test	P=0.507N	P=0.490N	P=0.342	P=0.500N
Logistic regression test	P=0.507N	P=0.490N	P=0.342	P=0.500N
Cochran-Armitage test	P=0.505N			
Fisher exact test		P=0.480N	P=0.303	P=0.492N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	6/63 (10%)	9/66 (14%)	8/61 (13%)	6/62 (10%)
Adjusted rate	14.1%	20.5%	18.8%	14.6%
Terminal rate	5/41 (12%)	7/40 (18%)	7/41 (17%)	4/38 (11%)
First incidence (days)	694	597	640	673
Life table test	P=0.504N	P=0.287	P=0.387	P=0.574
Logistic regression test	P=0.469N	P=0.357	P=0.373	P=0.617N
Cochran-Armitage test	P=0.488N			
Fisher exact test		P=0.326	P=0.364	P=0.607
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	7/63 (11%)	9/66 (14%)	8/61 (13%)	7/62 (11%)
Adjusted rate	16.5%	20.5%	18.8%	16.5%
Terminal rate	6/41 (15%)	7/40 (18%)	7/41 (17%)	4/38 (11%)
First incidence (days)	694	597	640	673
Life table test	P=0.534N	P=0.388	P=0.498	P=0.564
Logistic regression test	P=0.497N	P=0.469	P=0.484	P=0.603N
Cochran-Armitage test	P=0.517N			
Fisher exact test		P=0.434	P=0.473	P=0.599
Spleen: Hemangiosarcoma				
Overall rate	2/64 (3%)	2/66 (3%)	5/63 (8%)	2/63 (3%)
Adjusted rate	4.7%,	4.8%	10.7%	4.4%
Terminal rate	1/41 (2%)	1/40 (3%)	3/42 (7%)	0/38 (0%)
First incidence (days)	728	720	538	658
Life table test	P=0.496	P=0.679	P=0.230	P=0.678
Logistic regression test	P=0.520	P=0.693N	P=0.220	P=0.683N
Cochran-Armitage test	P=0.504			
Fisher exact test		P=0.679N	P=0.213	P=0.685
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	3/62 (5%)	1/66 (2%)	1/63 (2%)	1/64 (2%)
Adjusted rate	7.3%	2.3%	2.4%	2.1%
Terminal rate	3/41 (7%)	0/40 (0%)	1/42 (2%)	0/38 (0%)
First incidence (days)	729 (T)	711	729 (T)	658
Life table test	P=0.258N	P=0.313N	P=0.297N	P=0.323N
Logistic regression test	P=0.245N	P=0.294N	P=0.297N	P=0.294N
Cochran-Armitage test	P=0.241N			
Fisher exact test		P=0.286N	P=0.303N	P=0.298N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
Uterus: Stromal Polyp				
Overall rate	2/64 (3%)	4/66 (6%)	0/63 (0%)	1/64 (2%)
Adjusted rate	4.3%	8.3%	0.0%	2.6%
Terminal rate	1/41 (2%)	2/40 (5%)	0/42 (0%)	1/38 (3%)
First incidence (days)	559	583	—	729 (T)
Life table test	P=0.204N	P=0.361	P=0.235N	P=0.513N
Logistic regression test	P=0.193N	P=0.359	P=0.240N	P=0.489N
Cochran-Armitage test	P=0.198N			
Fisher exact test		P=0.355	P=0.252N	P=0.500N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	3/64 (5%)	4/66 (6%)	1/63 (2%)	1/64 (2%)
Adjusted rate	6.7%	8.3%	2.4%	2.6%
Terminal rate	2/41 (5%)	2/40 (5%)	1/42 (2%)	1/38 (3%)
First incidence (days)	559	583	729 (T)	729 (T)
Life table test	P=0.145N	P=0.519	P=0.299N	P=0.324N
Logistic regression test	P=0.132N	P=0.532	P=0.304N	P=0.291N
Cochran-Armitage test	P=0.138N			
Fisher exact test		P=0.517	P=0.315N	P=0.310N
Uterus: Hemangiosarcoma				
Overall rate	0/64 (0%)	3/66 (5%)	1/63 (2%)	1/64 (2%)
Adjusted rate	0.0%	6.9%	2.3%	2.6%
Terminal rate	0/41 (0%)	2/40 (5%)	0/42 (0%)	1/38 (3%)
First incidence (days)	—	657	681	729 (T)
Life table test	P=0.583	P=0.125	P=0.487	P=0.485
Logistic regression test	P=0.602	P=0.136	P=0.501	P=0.485
Cochran-Armitage test	P=0.594			
Fisher exact test		P=0.128	P=0.496	P=0.500
All Organs: Hemangiosarcoma				
Overall rate	3/64 (5%)	6/66 (9%)	8/63 (13%)	4/64 (6%)
Adjusted rate	7.1%	13.2%	17.3%	8.7%
Terminal rate	2/41 (5%)	3/40 (8%)	5/42 (12%)	1/38 (3%)
First incidence (days)	728	640	538	640
Life table test	P=0.459	P=0.249	P=0.112	P=0.483
Logistic regression test	P=0.497	P=0.285	P=0.104	P=0.523
Cochran-Armitage test	P=0.477			
Fisher exact test		P=0.262	P=0.098	P=0.500
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	3/64 (5%)	6/66 (9%)	9/63 (14%)	5/64 (8%)
Adjusted rate	7.1%	13.2%	18.9%	11.2%
Terminal rate	2/41 (5%)	3/40 (8%)	5/42 (12%)	2/38 (5%)
First incidence (days)	728	640	538	640
Life table test	P=0.320	P=0.249	P=0.073	P=0.340
Logistic regression test	P=0.353	P=0.285	P=0.065	P=0.378
Cochran-Armitage test	P=0.334			
Fisher exact test		P=0.262	P=0.060	P=0.359

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
All Organs: Malignant Lymphoma				
Overall rate	13/64 (20%)	12/66 (18%)	9/63 (14%)	7/64 (11%)
Adjusted rate	28.6%	25.3%	18.7%	15.8%
Terminal rate	9/41 (22%)	6/40 (15%)	5/42 (12%)	4/38 (11%)
First incidence (days)	618	597	321	426
Life table test	P=0.096N	P=0.506N	P=0.239N	P=0.145N
Logistic regression test	P=0.065N	P=0.405N	P=0.237N	P=0.090N
Cochran-Armitage test	P=0.075N			
Fisher exact test		P=0.466N	P=0.254N	P=0.111N
All Organs: Benign Neoplasms				
Overall rate	21/64 (33%)	28/66 (42%)	28/63 (44%)	24/64 (38%)
Adjusted rate	44.8%	55.9%	55.9%	53.0%
Terminal rate	16/41 (39%)	19/40 (48%)	20/42 (48%)	17/38 (45%)
First incidence (days)	92	162	587	619
Life table test	P=0.343	P=0.153	P=0.167	P=0.278
Logistic regression test	P=0.462	P=0.214	P=0.137	P=0.313
Cochran-Armitage test	P=0.403			
Fisher exact test		P=0.171	P=0.122	P=0.356
All Organs: Malignant Neoplasms				
Overall rate	30/64 (47%)	37/66 (56%)	28/63 (44%)	28/64 (44%)
Adjusted rate	61.0%	64.6%	51.2%	49.9%
Terminal rate	22/41 (54%)	20/40 (50%)	16/42 (38%)	11/38 (29%)
First incidence (days)	586	469	321	426
Life table test	P=0.315N	P=0.192	P=0.410N	P=0.503N
Logistic regression test	P=0.085N	P=0.297	P=0.343N	P=0.332N
Cochran-Armitage test	P=0.234N			
Fisher exact test		P=0.192	P=0.461N	P=0.430N
All Organs: Benign or Malignant Neoplasms				
Overall rate	37/64 (58%)	50/66 (76%)	45/63 (71%)	40/64 (63%)
Adjusted rate	70.8%	80.6%	77.6%	72.2%
Terminal rate	26/41 (63%)	28/40 (70%)	29/42 (69%)	23/38 (61%)
First incidence (days)	92	162	321	426
Life table test	P=0.456	P=0.052	P=0.174	P=0.300
Logistic regression test	P=0.308N	P=0.047	P=0.093	P=0.479
Cochran-Armitage test	P=0.533N			
Fisher exact test		P=0.023	P=0.078	P=0.359

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, ovary, pituitary gland, spleen, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE D4
Historical Incidence of Alveolar/bronchiolar Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Lovelace Inhalation Toxicology Research Institute			
Nickel Oxide	2/64	4/64	6/64
Nickel Subsulfide	3/58	7/58	9/58
Nickel Sulfate Hexahydrate	3/61	4/61	7/61
Talc	3/46	2/46	5/46
Overall Historical Incidence in Inhalation Studies			
Total	6/944 (6.5%)	38/944 (4.0%)	97/944 (10.3%)
Standard deviation	3/1%	3.2%	3.7%
Range	0%-14%	0%-12%	0%-16%
Overall Historical Incidence in Feed Studies			
Total	78/1,319 (5.9%)	26/1,319 (2.0%)	102/1,319 (7.7%)
Standard deviation	5.0%	2.3%	5.3%
Range	0%-24%	0%-8%	2%-26%

[a] Data as of 17 June 1994

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
Disposition Summary				
Animals initially in study	74	76	74	75
7-Month interim evaluation	5	5	5	5
15-Month interim evaluation	5	5	5	5
Early deaths				
Accidental deaths	1		1	
Moribund	15	18	9	16
Natural deaths	7	8	11	10
Survivors				
Terminal sacrifice	40	38	42	38
Died last week of study	1	2		
Pregnant/Missexed			1	1
Animals examined microscopically	74	76	73	74
7-Month Interim Evaluation				
Genital System				
Uterus				(1)
Inflammation, suppurative				1 (100%)
Hematopoietic System				
Lymph node, bronchial	(3)	(4)	(5)	(5)
Hyperplasia		1 (25%)		
Pigmentation		1 (25%)	5 (100%)	5 (100%)
Lymph node, mandibular		(1)		
Hyperplasia, lymphoid		1 (100%)		
Lymph node, mediastinal		(2)		(2)
Hyperplasia		1 (50%)		
Spleen		(1)		
Hyperplasia, lymphoid		1 (100%)		
Respiratory System				
Lung	(5)	(5)	(5)	(5)
Inflammation, chronic		1 (20%)	4 (80%)	4 (80%)
Alveolus, pigmentation		4 (80%)	5 (100%)	5 (100%)
Nose	(5)	(5)	(5)	(5)
Olfactory epithelium, degeneration	1 (20%)			
Respiratory epithelium, degeneration	1 (20%)			
Urinary System				
Kidney	(5)	(5)	(5)	(5)
Infiltration cellular, lymphocyte	1 (20%)	2 (40%)	1 (20%)	2 (40%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
7-Month Interim Evaluation (continued)				
Systems Examined With No Lesions Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
15-Month Interim Evaluation				
Alimentary System				
Liver	(5)	(5)	(5)	(5)
Infiltration cellular, lymphocyte			1 (20%)	
Inflammation, chronic		1 (20%)		
Cardiovascular System				
Heart	(5)	(5)	(5)	(5)
Venule, inflammation, chronic active				1 (20%)
Endocrine System				
Adrenal cortex	(5)	(5)	(5)	(5)
Infiltration cellular	1 (20%)			
Pituitary gland	(5)	(5)	(5)	(5)
Pars distalis, angiectasis			1 (20%)	
Genital System				
Ovary	(5)	(5)	(5)	(5)
Cyst		1 (20%)		
Uterus	(5)	(5)	(5)	(5)
Bilateral, endometrium, hyperplasia	1 (20%)			
Endometrium, hyperplasia	3 (60%)	5 (100%)	5 (100%)	5 (100%)
Hematopoietic System				
Lymph node, bronchial	(5)	(5)	(5)	(5)
Hyperplasia, lymphoid		3 (60%)	4 (80%)	4 (80%)
Pigmentation		4 (80%)	5 (100%)	5 (100%)
Lymph node, mandibular	(5)	(5)	(5)	(5)
Hyperplasia, lymphoid		2 (40%)		
Lymph node, mediastinal	(2)	(4)	(3)	(2)
Hyperplasia, lymphoid		1 (25%)		
Spleen	(5)	(5)	(5)	(5)
Hyperplasia, lymphoid	1 (20%)	2 (40%)	1 (20%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(5)	(5)	(5)	(5)
Inflammation, chronic		2 (40%)	4 (80%)	4 (80%)
Bronchialization[b]			3 (60%)	3 (60%)
Alveolus, pigmentation		4 (80%)	5 (100%)	5 (100%)
Alveolus, proteinosis				3 (60%)
Nose	(5)	(5)	(5)	(5)
Olfactory epithelium, degeneration	2 (40%)			
Respiratory epithelium, degeneration	1 (20%)	1 (20%)	2 (40%)	3 (60%)
Special Senses System				
Ear				(1)
External ear, hemorrhage				1 (100%)
Systems Examined With No Lesions Observed				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Urinary System				
2-Year Study				
Alimentary System				
Gallbladder	(60)	(59)	(57)	(56)
Inflammation, suppurative			1 (2%)	
Intestine large, cecum	(60)	(60)	(57)	(56)
Hyperplasia, lymphoid	1 (2%)		4 (7%)	1 (2%)
Intestine small, duodenum	(60)	(60)	(56)	(56)
Hyperplasia, lymphoid			2 (4%)	
Inflammation, suppurative		1 (2%)		
Intestine small, ileum	(58)	(57)	(56)	(54)
Hyperplasia, lymphoid			2 (4%)	
Liver	(64)	(66)	(63)	(63)
Abscess	1 (2%)			
Basophilic focus	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Clear cell focus	2 (3%)		1 (2%)	1 (2%)
Eosinophilic focus	2 (3%)		2 (3%)	
Inflammation, chronic	1 (2%)			
Inflammation, chronic, focal	1 (2%)	3 (5%)	3 (5%)	
Mixed cell focus			1 (2%)	
Hepatocyte, fatty change			1 (2%)	
Hepatocyte, hyperplasia		1 (2%)		
Hepatocyte, necrosis		1 (2%)	1 (2%)	3 (5%)
Hepatocyte, vacuolization cytoplasmic	1 (2%)	1 (2%)		
Sinusoid, amyloid deposition		1 (2%)		
Mesentery	(2)	(2)	(1)	(3)
Inflammation, chronic active				1 (33%)
Artery, inflammation, chronic		2 (100%)		
Fat, necrosis				1 (33%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(64)	(66)	(62)	(62)
Atrophy			1 (2%)	
Congestion			1 (2%)	
Cyst			1 (2%)	
Infiltration cellular, lymphocyte			1 (2%)	
Inflammation, chronic		1 (2%)		
Inflammation, suppurative			1 (2%)	
Stomach, forestomach	(64)	(63)	(62)	(60)
Hyperkeratosis	1 (2%)	8 (13%)	2 (3%)	1 (2%)
Hyperplasia, squamous				1 (2%)
Inflammation, chronic	1 (2%)			
Inflammation, suppurative		1 (2%)		
Stomach, glandular	(63)	(63)	(62)	(60)
Inflammation, chronic	1 (2%)			
Inflammation, suppurative		1 (2%)		
Tooth	(2)	(1)	(1)	(2)
Developmental malformation	1 (50%)	1 (100%)		1 (50%)
Inflammation	1 (50%)		1 (100%)	
Cardiovascular System				
Heart	(64)	(66)	(63)	(64)
Inflammation, chronic active			1 (2%)	
Inflammation, suppurative			1 (2%)	
Arteriole, inflammation, chronic	1 (2%)			
Endocrine System				
Adrenal cortex	(64)	(66)	(63)	(62)
Hyperplasia	1 (2%)	2 (3%)	1 (2%)	1 (2%)
Vacuolization cytoplasmic	1 (2%)			
Spindle cell, hyperplasia	4 (6%)	2 (3%)		1 (2%)
Adrenal medulla	(62)	(65)	(63)	(62)
Degeneration	1 (2%)			
Hyperplasia	1 (2%)			
Spindle cell, hyperplasia	1 (2%)	2 (3%)		
Islets, pancreatic	(63)	(65)	(62)	(62)
Hyperplasia		1 (2%)		
Pituitary gland	(63)	(66)	(61)	(62)
Pars distalis, angiectasis	7 (11%)	10 (15%)	11 (18%)	7 (11%)
Pars distalis, hyperplasia	10 (16%)	9 (14%)	4 (7%)	9 (15%)
Pars distalis, necrosis				1 (2%)
Thyroid gland	(62)	(66)	(63)	(64)
Hyperplasia, cystic	26 (42%)	26 (39%)	32 (51%)	26 (41%)
Infiltration cellular, lymphocyte	1 (2%)			
Inflammation, suppurative		2 (3%)		
General Body System				
None				

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Oxide
(continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
2-Year Study (continued)				
Genital System				
Clitoral gland	(57)	(62)	(57)	(55)
Ectasia	1 (2%)	2 (3%)		3 (5%)
Inflammation, chronic	2 (4%)			1 (2%)
Inflammation, chronic active				1 (2%)
Pigmentation	5 (9%)	4 (6%)	5 (9%)	12 (22%)
Ovary	(61)	(66)	(60)	(63)
Abscess	2 (3%)			
Angiectasis				2 (3%)
Congestion		1 (2%)		
Cyst	8 (13%)	14 (21%)	9 (15%)	7 (11%)
Inflammation, suppurative	1 (2%)		1 (2%)	
Rete ovarii, thrombosis	1 (2%)			
Uterus	(64)	(66)	(62)	(63)
Cyst			1 (2%)	
Dilatation		1 (2%)		
Inflammation, suppurative	1 (2%)			1 (2%)
Bilateral, dilatation		1 (2%)		
Endometrium, hyperplasia, cystic	24 (38%)	34 (52%)	30 (48%)	29 (46%)
Hematopoietic System				
Bone marrow	(64)	(65)	(62)	(63)
Myelofibrosis	3 (5%)	2 (3%)		2 (3%)
Necrosis		1 (2%)	1 (2%)	
Myeloid cell, hyperplasia	5 (8%)	4 (6%)	3 (5%)	1 (2%)
Lymph node	(15)	(9)	(10)	(9)
Iliac, hyperplasia, lymphoid	3 (20%)	2 (22%)	1 (10%)	1 (11%)
Iliac, hyperplasia, macrophage				1 (11%)
Iliac, pigmentation		1 (11%)		
Pancreatic, hyperplasia, lymphoid			1 (10%)	1 (11%)
Renal, hyperplasia, lymphoid	4 (27%)	1 (11%)	1 (10%)	2 (22%)
Renal, inflammation, chronic active				1 (11%)
Lymph node, bronchial	(54)	(63)	(59)	(62)
Congestion		2 (3%)	1 (2%)	2 (3%)
Hyperplasia, lymphoid	14 (26%)	37 (59%)	40 (68%)	44 (71%)
Pigmentation		58 (92%)	56 (95%)	60 (97%)
Lymph node, mandibular	(61)	(63)	(59)	(58)
Congestion		1 (2%)	1 (2%)	
Hyperplasia, lymphoid	16 (26%)	18 (29%)	18 (31%)	14 (24%)
Hyperplasia, macrophage		1 (2%)		
Inflammation, suppurative			1 (2%)	
Lymph node, mesenteric	(54)	(63)	(54)	(55)
Congestion		4 (6%)	1 (2%)	1 (2%)
Ectasia		1 (2%)		
Hematopoietic cell proliferation				1 (2%)
Hyperplasia, lymphoid	8 (15%)	3 (5%)	8 (15%)	13 (24%)
Inflammation			1 (2%)	
Inflammation, chronic active			1 (2%)	
Inflammation, suppurative	1 (2%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mediastinal	(35)	(28)	(33)	(29)
Hyperplasia, lymphoid	1 (3%)	3 (11%)	3 (9%)	2 (7%)
Pigmentation		2 (7%)	1 (3%)	5 (17%)
Spleen	(64)	(66)	(63)	(63)
Congestion				2 (3%)
Hematopoietic cell proliferation	8 (13%)	6 (9%)	8 (13%)	5 (8%)
Hyperplasia, lymphoid	12 (19%)	17 (26%)	22 (35%)	17 (27%)
Hyperplasia, macrophage		1 (2%)		1 (2%)
Thymus	(59)	(61)	(60)	(57)
Atrophy	1 (2%)		1 (2%)	
Hyperplasia, lymphoid	1 (2%)			
Integumentary System				
Mammary gland	(63)	(66)	(63)	(63)
Hyperplasia, glandular	6 (10%)	4 (6%)	8 (13%)	8 (13%)
Skin	(4)	(8)	(6)	(12)
Alopecia		1 (13%)	1 (17%)	1 (8%)
Edema				1 (8%)
Hemorrhage				2 (17%)
Inflammation, chronic				1 (8%)
Inflammation, chronic active	1 (25%)			
Inflammation, suppurative			1 (17%)	
Epidermis, inflammation, suppurative				1 (8%)
Pinna, cyst epithelial inclusion		1 (13%)		
Subcutaneous tissue, edema	1 (25%)	1 (13%)		
Subcutaneous tissue, inflammation, chronic active				1 (8%)
Subcutaneous tissue, inflammation, suppurative			1 (17%)	
Subcutaneous tissue, necrosis				1 (8%)
Musculoskeletal System				
Bone	(64)	(65)	(63)	(63)
Fracture	1 (2%)			
Hyperostosis	17 (27%)	25 (38%)	26 (41%)	24 (38%)
Pelvis, fracture				1 (2%)
Nervous System				
Brain	(64)	(66)	(63)	(64)
Hypothalamus, compression		2 (3%)	6 (10%)	4 (6%)
Pons, compression		1 (2%)		
Spinal cord		(1)		
Hemorrhage		1 (100%)		
Respiratory System				
Larynx	(62)	(63)	(62)	(63)
Inflammation, suppurative		1 (2%)	1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nickel Oxide (continued)

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
2-Year Study (continued)				
Respiratory System (continued)				
Lung	(64)	(66)	(63)	(64)
Fibrosis			1 (2%)	3 (5%)
Hemorrhage		2 (3%)		
Inflammation, chronic	7 (11%)	43 (65%)	53 (84%)	52 (81%)
Inflammation, chronic active			1 (2%)	
Metaplasia, squamous				1 (2%)
Pigmentation, hemosiderin	2 (3%)			
Bronchialization[b]		35 (53%)	39 (62%)	40 (63%)
Alveolar epithelium, hyperplasia, focal			1 (2%)	
Alveolus, hemorrhage			1 (2%)	
Alveolus, hyperplasia, macrophage	1 (2%)	2 (3%)		
Alveolus, pigmentation		64 (97%)	61 (97%)	64 (100%)
Alveolus, proteinosis		8 (12%)	17 (27%)	29 (45%)
Nose	(62)	(65)	(62)	(62)
Inflammation, suppurative		1 (2%)		
Capillary, thrombosis	1 (2%)			
Olfactory epithelium, degeneration	16 (26%)	10 (15%)	2 (3%)	7 (11%)
Respiratory epithelium, degeneration	19 (31%)	15 (23%)	11 (18%)	17 (27%)
Respiratory epithelium, hyperplasia	1 (2%)	1 (2%)		
Respiratory epithelium, inflammation, chronic		1 (2%)		
Respiratory epithelium, inflammation, suppurative	17 (27%)	18 (28%)	18 (29%)	21 (34%)
Respiratory epithelium, metaplasia, squamous	10 (16%)	9 (14%)	14 (23%)	15 (24%)
Special Senses System				
Ear	(2)	(1)	(1)	(1)
External ear, hyperkeratosis		1 (100%)		
Eye				(2)
Cornea, inflammation				2 (100%)
Urinary System				
Kidney	(64)	(66)	(63)	(63)
Hydronephrosis	1 (2%)			
Infiltration cellular, lymphocyte			2 (3%)	
Inflammation, chronic		1 (2%)	2 (3%)	
Metaplasia, osseous	1 (2%)			
Necrosis				1 (2%)
Nephropathy	2 (3%)	3 (5%)	3 (5%)	2 (3%)
Cortex, cyst				1 (2%)
Glomerulus, thrombosis	1 (2%)			
Medulla, cyst			1 (2%)	
Pelvis, infiltration cellular, lymphocyte		1 (2%)		
Renal tubule, hyperplasia	1 (2%)			
Urethra				(1)
Concretion				1 (100%)
Urinary bladder	(63)	(62)	(60)	(57)
Inflammation, suppurative			1 (2%)	

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] This alteration is associated with injury to the parenchyma around the terminal bronchiole. It is listed as "alveolar epithelial hyperplasia" in the TDMS data tables for mice in this study.

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented in MacGregor *et al.* (1990). At the end of the 13-week toxicity study, peripheral blood samples were obtained from male and female B6C3F_1 mice and smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983) and coded. Ten thousand normochromatic erythrocytes (NCEs) were scored in each of 10 animals per dose group. The criteria of Schmid (1976) were used to define micronuclei.

The results were tabulated as the mean of the pooled results from all animals within a treatment group, plus or minus the standard error of the mean. The frequency of micronucleated cells among NCEs was analyzed by a statistical software package that tested for increasing trend over exposure groups using a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each exposure group and the control group (Margolin *et al.*, 1990). In the presence of excess binomial variation, as detected by à binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if 1) the trend test P value is less than or equal to 0.025 or 2) the P value for any single exposure group is less than or equal to 0.025/N where N equals the number of exposure groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, reproducibility of any effects observed, and the magnitudes of those effects.

RESULTS

Nickel oxide was tested for induction of micronuclei in normochromatic erythrocytes of male and female mice exposed by inhalation for 13 weeks. The compound did not induce an increase in the frequency of micronucleated NCEs in peripheral blood samples (Table E1).

TABLE E1
Frequency of Micronuclei in Mouse Peripheral Blood Erythrocytes Following Treatment with Nickel Oxide by Inhalation for 13 Weeks[a]

	Dose (mg/m^3)	Micronucleated Normochromatic Erythrocytes/1,000 Cells[b]	Number of Mice
Male			
	0	0.946 ± 1.26	10
	1.3	0.809 ± 1.03	10
	2.5	0.987 ± 0.91	10
	5.0	0.954 ± 0.89	10
Trend test		P=0.319[c]	
Female			
	0	0.548 ± 0.88	10
	1.3	0.504 ± 0.64	10
	2.5	0.697 ± 0.47	10
	5.0	0.571 ± 0.57	10
Trend test		P=0.295	
Urethane[d]	0.2	13.376 ± 0.724*	

* P<0.001
[a] Slides scored at SRI, International. The detailed protocol and these data are presented by MacGregor *et al.* (1990); 10,000 NCEs scored per animal.
[b] Data presented as mean ± standard error of the mean. NCE = normochromatic erythrocyte.
[c] Significance of micronucleated NCEs determined by a one-tailed Cochran-Armitage trend test.
[d] Urethane was used as the positive control and the dose is presented in parts per million.

APPENDIX F
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Inhalation Study of Nickel Oxide[a]

	0 mg/m³	1.2 mg/m³	2.5 mg/m³	5 mg/m³	10 mg/m³	30 mg/m³
n	5	5	5	5	5	5
Male						
Necropsy body wt	213 ± 5	211 ± 4	214 ± 6	210 ± 4	210 ± 4	204 ± 5
Brain						
Absolute	1.744 ± 0.022	1.774 ± 0.010	1.748 ± 0.017	1.732 ± 0.017	1.726 ± 0.019	1.710 ± 0.019
Relative	8.20 ± 0.15	8.42 ± 0.12	8.17 ± 0.16	8.24 ± 0.10	8.22 ± 0.17	8.42 ± 0.18
Heart						
Absolute	0.818 ± 0.037	0.782 ± 0.044	0.840 ± 0.047	0.846 ± 0.070	0.780 ± 0.022	0.834 ± 0.039
Relative	3.84 ± 0.15	3.71 ± 0.23	3.91 ± 0.16	4.02 ± 0.30	3.72 ± 0.15	4.13 ± 0.31
R. Kidney						
Absolute	0.851 ± 0.034	0.842 ± 0.025	0.883 ± 0.047	0.817 ± 0.022	0.806 ± 0.033	0.807 ± 0.023
Relative	3.99 ± 0.14	3.99 ± 0.11	4.12 ± 0.21	3.89 ± 0.11	3.83 ± 0.09	3.97 ± 0.07
Liver						
Absolute	10.020 ± 0.291	10.080 ± 0.159	9.780 ± 0.426	9.840 ± 0.121	10.040 ± 0.339	9.280 ± 0.267
Relative	47.03 ± 0.71	47.83 ± 0.99	45.58 ± 1.33	46.84 ± 0.81	47.73 ± 1.19	45.58 ± 0.28
Lung						
Absolute	1.060 ± 0.040	1.000 ± 0.032	1.060 ± 0.040	0.960 ± 0.024	1.200 ± 0.032*	1.360 ± 0.051**
Relative	4.98 ± 0.20	4.74 ± 0.14	4.94 ± 0.15	4.56 ± 0.07	5.72 ± 0.24**	6.68 ± 0.13**
Testes						
Absolute	1.188 ± 0.013	1.214 ± 0.016	1.258 ± 0.046	1.210 ± 0.033	1.242 ± 0.017	1.222 ± 0.025
Relative	5.59 ± 0.09	5.76 ± 0.12	5.87 ± 0.19	5.76 ± 0.16	5.92 ± 0.16	6.01 ± 0.05
Thymus						
Absolute	0.351 ± 0.008	0.363 ± 0.015	0.353 ± 0.011	0.323 ± 0.024	0.369 ± 0.009	0.341 ± 0.029
Relative	1.65 ± 0.05	1.72 ± 0.07	1.66 ± 0.09	1.54 ± 0.12	1.76 ± 0.06	1.67 ± 0.11
Female						
Necropsy body wt	150 ± 2	155 ± 3	154 ± 4	156 ± 2	150 ± 2	149 ± 3
Brain						
Absolute	1.650 ± 0.013	1.652 ± 0.020	1.662 ± 0.019	1.652 ± 0.018	1.702 ± 0.022	1.634 ± 0.047
Relative	11.03 ± 0.17	10.71 ± 0.22	10.83 ± 0.20	10.63 ± 0.20	11.32 ± 0.14	10.99 ± 0.29
Heart						
Absolute	0.558 ± 0.016	0.600 ± 0.024	0.602 ± 0.023	0.620 ± 0.011	0.590 ± 0.030	0.620 ± 0.027
Relative	3.73 ± 0.09	3.88 ± 0.09	3.92 ± 0.12	3.99 ± 0.11	3.92 ± 0.15	4.16 ± 0.14
R. Kidney						
Absolute	0.624 ± 0.007	0.642 ± 0.014	0.599 ± 0.024	0.608 ± 0.014	0.637 ± 0.025	0.628 ± 0.017
Relative	4.17 ± 0.05	4.16 ± 0.11	3.89 ± 0.13	3.91 ± 0.09	4.24 ± 0.16	4.22 ± 0.08
Liver						
Absolute	5.900 ± 0.164	6.560 ± 0.178	6.440 ± 0.238	5.980 ± 0.153	6.120 ± 0.235	5.520 ± 0.208
Relative	39.40 ± 0.78	42.48 ± 0.89	41.88 ± 1.18	38.43 ± 0.74	40.64 ± 1.07	37.06 ± 0.94
Lung						
Absolute	0.780 ± 0.020	0.860 ± 0.040	0.900 ± 0.032	0.820 ± 0.020	1.040 ± 0.024**	1.120 ± 0.037**
Relative	5.21 ± 0.11	5.56 ± 0.18	5.86 ± 0.21	5.27 ± 0.14	6.91 ± 0.12**	7.52 ± 0.11**
Thymus						
Absolute	0.293 ± 0.011	0.323 ± 0.019	0.301 ± 0.015	0.300 ± 0.012	0.291 ± 0.015	0.302 ± 0.021
Relative	1.95 ± 0.07	2.09 ± 0.11	1.95 ± 0.06	1.93 ± 0.06	1.93 ± 0.08	2.02 ± 0.12

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Inhalation Study of Nickel Oxide[a]

	0 mg/m³	0.6 mg/m³	1.2 mg/m³	2.5 mg/m³	5 mg/m³	10 mg/m³
Male						
n	10	10	10	9	10	10
Necropsy body wt	310 ± 8	312 ± 6	314 ± 6	297 ± 5	304 ± 6	301 ± 5
Brain						
Absolute	1.853 ± 0.019	1.893 ± 0.018	1.904 ± 0.023	1.849 ± 0.018	1.870 ± 0.019	1.880 ± 0.010
Relative	6.00 ± 0.12	6.08 ± 0.08	6.08 ± 0.09	6.23 ± 0.07	6.17 ± 0.12	6.26 ± 0.08
Heart						
Absolute	0.902 ± 0.029	0.898 ± 0.024	0.926 ± 0.023	0.852 ± 0.031	0.894 ± 0.029	0.911 ± 0.015
Relative	2.91 ± 0.06	2.88 ± 0.07	2.95 ± 0.06	2.86 ± 0.07	2.94 ± 0.07	3.03 ± 0.06
R. Kidney						
Absolute	1.029 ± 0.038	1.052 ± 0.026	1.064 ± 0.028	0.991 ± 0.015	0.984 ± 0.022	1.042 ± 0.019
Relative	3.32 ± 0.10	3.38 ± 0.10	3.39 ± 0.07	3.34 ± 0.06	3.24 ± 0.06	3.46 ± 0.05
Liver						
Absolute	10.560 ± 0.392	11.150 ± 0.202	10.880 ± 0.235	10.644 ± 0.245	10.430 ± 0.238	10.720 ± 0.199
Relative	34.06 ± 0.93	35.77 ± 0.33	34.69 ± 0.31	35.84 ± 0.58	34.29 ± 0.44	35.63 ± 0.51
Lung						
Absolute	1.180 ± 0.037	1.349 ± 0.024**	1.474 ± 0.041**	1.698 ± 0.053**	1.906 ± 0.032**	2.467 ± 0.045**
Relative	3.81 ± 0.11	4.33 ± 0.09**	4.70 ± 0.11**	5.73 ± 0.19**	6.27 ± 0.05**	8.21 ± 0.19**
R. Testis						
Absolute	1.340 ± 0.028	1.429 ± 0.024	1.479 ± 0.054	1.438 ± 0.037	1.418 ± 0.034	1.455 ± 0.054
Relative	4.34 ± 0.12	4.60 ± 0.12	4.72 ± 0.15	4.84 ± 0.10*	4.67 ± 0.12*	4.84 ± 0.17*
Thymus						
Absolute	0.283 ± 0.014	0.281 ± 0.018	0.266 ± 0.006	0.254 ± 0.015	0.249 ± 0.004	0.259 ± 0.010
Relative	0.92 ± 0.06	0.90 ± 0.05	0.85 ± 0.02	0.86 ± 0.05	0.82 ± 0.01	0.86 ± 0.04
Female						
n	10	10	10	10	10	10
Necropsy body wt	192 ± 6	182 ± 6	189 ± 3	192 ± 4	189 ± 5	195 ± 5
Brain						
Absolute	1.791 ± 0.030	1.685 ± 0.060	1.767 ± 0.011	1.765 ± 0.019	1.740 ± 0.025	1.766 ± 0.021
Relative	9.38 ± 0.15	9.35 ± 0.45	9.35 ± 0.13	9.21 ± 0.15	9.26 ± 0.23	9.10 ± 0.16
Heart						
Absolute	0.663 ± 0.021	0.606 ± 0.008	0.659 ± 0.014	0.688 ± 0.039	0.604 ± 0.013	0.672 ± 0.020
Relative	3.47 ± 0.08	3.36 ± 0.11	3.49 ± 0.09	3.58 ± 0.20	3.20 ± 0.05	3.45 ± 0.07
R. Kidney						
Absolute	0.667 ± 0.021	0.661 ± 0.015	0.664 ± 0.014	0.667 ± 0.019	0.642 ± 0.016	0.688 ± 0.017
Relative	3.49 ± 0.11	3.66 ± 0.12	3.51 ± 0.05	3.47 ± 0.09	3.41 ± 0.07	3.54 ± 0.06
Liver						
Absolute	6.730 ± 0.171	5.870 ± 0.360*	6.540 ± 0.115	6.740 ± 0.194	6.300 ± 0.180	6.890 ± 0.161
Relative	35.17 ± 0.35	32.00 ± 1.17**	34.57 ± 0.52	35.04 ± 0.51	33.38 ± 0.51	35.41 ± 0.30
Lung						
Absolute	0.983 ± 0.026	1.027 ± 0.023	1.134 ± 0.024*	1.550 ± 0.038**	1.610 ± 0.047**	2.111 ± 0.081**
Relative	5.14 ± 0.10	5.68 ± 0.17*	6.00 ± 0.11**	8.06 ± 0.10**	8.55 ± 0.23**	10.84 ± 0.31**
Thymus						
Absolute	0.241 ± 0.008	0.224 ± 0.008	0.219 ± 0.007	0.237 ± 0.007	0.229 ± 0.008	0.235 ± 0.009
Relative	1.26 ± 0.05	1.23 ± 0.03	1.16 ± 0.03	1.24 ± 0.04	1.21 ± 0.04	1.20 ± 0.02

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 7-Month Interim Evaluation in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Male				
n	6	7	7	7
Necropsy body wt	391 ± 10	390 ± 5	402 ± 9	407 ± 10
Brain				
Absolute	2.030 ± 0.016	2.004 ± 0.037	2.037 ± 0.017	2.061 ± 0.018
Relative	5.21 ± 0.12	5.14 ± 0.11	5.09 ± 0.12	5.08 ± 0.10
R. Kidney				
Absolute	1.293 ± 0.047	1.363 ± 0.036	1.404 ± 0.042	1.464 ± 0.040**
Relative	3.31 ± 0.10	3.49 ± 0.08	3.50 ± 0.07	3.61 ± 0.10
Liver				
Absolute	13.883 ± 1.071	14.131 ± 0.469	15.113 ± 0.595	16.559 ± 0.760*
Relative	35.44 ± 2.37	36.16 ± 0.82	37.62 ± 1.13	40.74 ± 1.78*
Lung				
Absolute	1.718 ± 0.072	1.850 ± 0.071	2.426 ± 0.107**	2.593 ± 0.060**
Relative	4.40 ± 0.14	4.74 ± 0.17	6.04 ± 0.22**	6.40 ± 0.24**
Spleen				
Absolute	0.773 ± 0.030	0.759 ± 0.023	0.757 ± 0.017	0.756 ± 0.022
Relative	1.98 ± 0.06	1.94 ± 0.05	1.89 ± 0.05	1.86 ± 0.04
R. Testis				
Absolute	1.508 ± 0.034	1.580 ± 0.025	1.541 ± 0.027	1.526 ± 0.033
Relative	3.87 ± 0.09	4.05 ± 0.06	3.84 ± 0.05	3.76 ± 0.12
Thymus				
Absolute	0.253 ± 0.027	0.272 ± 0.022	0.268 ± 0.031	0.272 ± 0.024
Relative	0.65 ± 0.07	0.70 ± 0.06	0.66 ± 0.06	0.67 ± 0.05
Female				
n	7	7	7	6
Necropsy body wt	234 ± 4	234 ± 2	236 ± 4	232 ± 6
Brain				
Absolute	1.857 ± 0.013	1.877 ± 0.018	1.880 ± 0.013	1.888 ± 0.014
Relative	7.95 ± 0.15	8.02 ± 0.08	7.98 ± 0.14	8.18 ± 0.21
R. Kidney				
Absolute	0.851 ± 0.029	0.886 ± 0.016	0.826 ± 0.040	0.845 ± 0.037
Relative	3.65 ± 0.17	3.79 ± 0.06	3.50 ± 0.15	3.64 ± 0.07
Liver				
Absolute	8.284 ± 0.314	8.829 ± 0.305	8.304 ± 0.391	8.502 ± 0.327
Relative	35.43 ± 1.31	37.72 ± 1.20	35.19 ± 1.49	36.72 ± 1.06
Lung				
Absolute	1.140 ± 0.028	1.310 ± 0.026*	1.647 ± 0.070**	1.777 ± 0.076**
Relative	4.89 ± 0.19	5.60 ± 0.09*	6.97 ± 0.22**	7.67 ± 0.22**
Spleen				
Absolute	0.526 ± 0.008	0.519 ± 0.009	0.529 ± 0.020	0.528 ± 0.014
Relative	2.25 ± 0.03	2.22 ± 0.04	2.25 ± 0.11	2.28 ± 0.04
Thymus				
Absolute	0.227 ± 0.023	0.212 ± 0.018	0.204 ± 0.013	0.176 ± 0.011
Relative	0.97 ± 0.09	0.90 ± 0.07	0.86 ± 0.05	0.76 ± 0.03

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
n	5	5	5	5
Male				
Necropsy body wt	494 ± 10	466 ± 14	465 ± 9	475 ± 12
Brain				
Absolute	2.102 ± 0.028	2.030 ± 0.016	2.074 ± 0.017	2.062 ± 0.018
Relative	4.26 ± 0.08	4.37 ± 0.14	4.46 ± 0.06	4.35 ± 0.13
R. Kidney				
Absolute	1.662 ± 0.026	1.574 ± 0.055	1.586 ± 0.028	1.554 ± 0.024
Relative	3.37 ± 0.05	3.37 ± 0.05	3.42 ± 0.11	3.28 ± 0.07
Liver				
Absolute	17.928 ± 0.474	16.170 ± 0.764	16.800 ± 0.548	16.534 ± 0.774
Relative	36.27 ± 0.41	34.67 ± 1.35	36.11 ± 0.85	34.73 ± 0.93
Lung				
Absolute	2.196 ± 0.038	2.154 ± 0.098	3.304 ± 0.163**	4.088 ± 0.117**
Relative	4.45 ± 0.12	4.63 ± 0.21	7.13 ± 0.45**	8.63 ± 0.35**
Spleen				
Absolute	1.054 ± 0.064	0.974 ± 0.072	0.964 ± 0.043	1.028 ± 0.040
Relative	2.13 ± 0.10	2.08 ± 0.12	2.07 ± 0.09	2.17 ± 0.12
Thymus				
Absolute	0.249 ± 0.011	0.240 ± 0.027	0.228 ± 0.019	0.255 ± 0.024
Relative	0.50 ± 0.02	0.52 ± 0.06	0.49 ± 0.03	0.54 ± 0.05
Female				
Necropsy body wt	290 ± 13	309 ± 15	284 ± 11	295 ± 11
Brain				
Absolute	1.862 ± 0.041	1.878 ± 0.030	1.850 ± 0.034	1.900 ± 0.016
Relative	6.46 ± 0.17	6.12 ± 0.20	6.54 ± 0.14	6.47 ± 0.23
R. Kidney				
Absolute	1.052 ± 0.036	1.106 ± 0.036	1.062 ± 0.046	1.022 ± 0.054
Relative	3.66 ± 0.19	3.61 ± 0.20	3.79 ± 0.31	3.47 ± 0.15
Liver				
Absolute	10.194 ± 0.834	10.392 ± 0.320	9.896 ± 0.154	9.708 ± 0.537
Relative	35.45 ± 3.37	33.76 ± 0.80	35.07 ± 1.30	32.90 ± 1.45
Lung				
Absolute	1.558 ± 0.107	1.788 ± 0.097	2.406 ± 0.106**	3.016 ± 0.127**
Relative	5.39 ± 0.36	5.85 ± 0.45	8.51 ± 0.40**	10.29 ± 0.69**
Spleen				
Absolute	0.556 ± 0.029	0.674 ± 0.040	0.526 ± 0.022	0.592 ± 0.063
Relative	1.93 ± 0.09	2.20 ± 0.15	1.86 ± 0.10	1.99 ± 0.16
Thymus				
Absolute	0.182 ± 0.012	0.216 ± 0.010	0.180 ± 0.019	0.203 ± 0.033
Relative	0.63 ± 0.05	0.71 ± 0.05	0.64 ± 0.08	0.68 ± 0.10

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Inhalation Study of Nickel Oxide[a]

	0 mg/m³	1.2 mg/m³	2.5 mg/m³	5 mg/m³	10 mg/m³	30 mg/m³
Male						
n	5	5	5	4	5	5
Necropsy body wt	23.9 ± 0.8	23.9 ± 0.5	23.8 ± 0.7	23.3 ± 0.5	24.4 ± 0.8	22.3 ± 0.4
Brain						
Absolute	0.452 ± 0.013	0.442 ± 0.006	0.444 ± 0.005	0.430 ± 0.017	0.438 ± 0.007	0.440 ± 0.005
Relative	19.04 ± 0.87	18.49 ± 0.39	18.67 ± 0.49	18.49 ± 0.86	18.03 ± 0.40	19.70 ± 0.18
Heart						
Absolute	0.152 ± 0.010	0.140 ± 0.007	0.174 ± 0.017	0.135 ± 0.019	0.144 ± 0.009	0.146 ± 0.007
Relative	6.38 ± 0.36	5.88 ± 0.39	7.27 ± 0.60	5.76 ± 0.71	5.91 ± 0.35	6.56 ± 0.41
R. Kidney						
Absolute	0.244 ± 0.005	0.210 ± 0.004*	0.254 ± 0.011	0.195 ± 0.006**	0.248 ± 0.012	0.214 ± 0.007
Relative	10.25 ± 0.24	8.78 ± 0.19**	10.65 ± 0.31	8.38 ± 0.29**	10.17 ± 0.22	9.57 ± 0.19
Liver						
Absolute	1.380 ± 0.073	1.280 ± 0.049	1.460 ± 0.081	1.325 ± 0.075	1.360 ± 0.068	1.160 ± 0.051
Relative	57.78 ± 1.89	53.42 ± 1.33	61.09 ± 2.01	56.75 ± 2.22	55.74 ± 1.37	51.86 ± 1.73
Lung						
Absolute	0.200 ± 0.000	0.160 ± 0.024	0.200 ± 0.000	0.125 ± 0.025**	0.200 ± 0.000	0.200 ± 0.000
Relative	8.42 ± 0.30	6.77 ± 1.14	8.42 ± 0.24	5.37 ± 1.06*	8.24 ± 0.26	8.96 ± 0.15
Testes						
Absolute	0.108 ± 0.007	0.100 ± 0.003	0.104 ± 0.005	0.110 ± 0.009	0.108 ± 0.006	0.110 ± 0.004
Relative	4.59 ± 0.47	4.19 ± 0.17	4.39 ± 0.31	4.73 ± 0.41	4.42 ± 0.12	4.92 ± 0.16
Thymus						
Absolute	0.045 ± 0.004	0.050 ± 0.004	0.049 ± 0.008	0.040 ± 0.007	0.051 ± 0.006	0.039 ± 0.004
Relative	1.92 ± 0.26	2.07 ± 0.15	2.04 ± 0.33	1.72 ± 0.31	2.11 ± 0.27	1.77 ± 0.20
Female						
n	5	5	5	5	5	5
Necropsy body wt	20.2 ± 0.5	20.2 ± 0.2	19.4 ± 0.6	20.2 ± 0.3	19.2 ± 0.3	19.3 ± 0.3
Brain						
Absolute	0.446 ± 0.009	0.432 ± 0.012	0.446 ± 0.005	0.444 ± 0.009	0.422 ± 0.016	0.438 ± 0.006
Relative	22.05 ± 0.37	21.43 ± 0.55	23.10 ± 0.94	22.00 ± 0.16	21.98 ± 1.02	22.74 ± 0.42
Heart						
Absolute	0.114 ± 0.010	0.132 ± 0.009	0.130 ± 0.016	0.128 ± 0.004	0.102 ± 0.005	0.110 ± 0.000
Relative	5.64 ± 0.49	6.54 ± 0.37	6.66 ± 0.72	6.35 ± 0.20	5.30 ± 0.25	5.71 ± 0.10
R. Kidney						
Absolute	0.148 ± 0.008	0.158 ± 0.005	0.156 ± 0.011	0.152 ± 0.005	0.148 ± 0.004	0.164 ± 0.007
Relative	7.31 ± 0.36	7.83 ± 0.19	8.01 ± 0.40	7.54 ± 0.23	7.70 ± 0.21	8.50 ± 0.30*
Liver						
Absolute	1.160 ± 0.075	1.220 ± 0.037	1.040 ± 0.040	1.140 ± 0.024	1.020 ± 0.037	1.080 ± 0.049
Relative	57.20 ± 2.91	60.48 ± 1.43	53.57 ± 0.94	56.52 ± 1.20	53.06 ± 2.01	55.98 ± 2.16
Lung						
Absolute	0.160 ± 0.024	0.160 ± 0.024	0.140 ± 0.024	0.180 ± 0.020	0.120 ± 0.020	0.200 ± 0.000
Relative	7.95 ± 1.27	7.91 ± 1.18	7.17 ± 1.16	8.96 ± 1.05	6.21 ± 0.96	10.39 ± 0.17
Thymus						
Absolute	0.064 ± 0.004	0.050 ± 0.004	0.059 ± 0.005	0.058 ± 0.002	0.052 ± 0.008	0.050 ± 0.004
Relative	3.19 ± 0.21	2.51 ± 0.19	3.06 ± 0.27	2.87 ± 0.13	2.70 ± 0.40	2.59 ± 0.20

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Inhalation Study of Nickel Oxide[a]

	0 mg/m³	0.6 mg/m³	1.2 mg/m³	2.5 mg/m³	5 mg/m³	10 mg/m³
Male						
n	10	10	10	10	10	9
Necropsy body wt	30.9 ± 0.5	30.5 ± 0.7	29.8 ± 0.4	30.1 ± 0.8	30.1 ± 0.9	29.1 ± 0.7
Brain						
Absolute	0.471 ± 0.007	0.462 ± 0.005	0.454 ± 0.005	0.458 ± 0.005	0.456 ± 0.005	0.464 ± 0.009
Relative	15.25 ± 0.25	15.17 ± 0.25	15.28 ± 0.21	15.33 ± 0.39	15.24 ± 0.38	15.99 ± 0.36
Heart						
Absolute	0.163 ± 0.007	0.170 ± 0.008	0.159 ± 0.004	0.144 ± 0.007	0.153 ± 0.005	0.149 ± 0.006
Relative	5.28 ± 0.24	5.59 ± 0.32	5.35 ± 0.15	4.80 ± 0.22	5.10 ± 0.18	5.11 ± 0.17
R. Kidney						
Absolute	0.316 ± 0.008	0.312 ± 0.011	0.309 ± 0.010	0.302 ± 0.016	0.301 ± 0.008	0.276 ± 0.011
Relative	10.22 ± 0.23	10.20 ± 0.23	10.39 ± 0.34	10.00 ± 0.32	10.02 ± 0.24	9.45 ± 0.32
Liver						
Absolute	1.710 ± 0.055	1.680 ± 0.071	1.550 ± 0.050	1.610 ± 0.098	1.520 ± 0.063	1.444 ± 0.065*
Relative	55.20 ± 1.17	54.82 ± 1.33	52.06 ± 1.33	53.10 ± 2.17	50.51 ± 1.64*	49.42 ± 1.29*
Lung						
Absolute	0.214 ± 0.009	0.215 ± 0.011	0.206 ± 0.012	0.213 ± 0.009	0.243 ± 0.010	0.288 ± 0.019**
Relative	6.96 ± 0.33	7.10 ± 0.48	6.93 ± 0.42	7.12 ± 0.29	8.06 ± 0.27	9.94 ± 0.68**
R. Testis						
Absolute	0.121 ± 0.005	0.118 ± 0.004	0.115 ± 0.003	0.112 ± 0.004	0.123 ± 0.004	0.106 ± 0.009
Relative	3.92 ± 0.16	3.87 ± 0.12	3.87 ± 0.11	3.75 ± 0.17	4.09 ± 0.08	3.61 ± 0.31
Thymus						
Absolute	0.034 ± 0.002	0.030 ± 0.003	0.031 ± 0.002	0.031 ± 0.003	0.032 ± 0.001	0.032 ± 0.002
Relative	1.10 ± 0.07	0.99 ± 0.10	1.03 ± 0.06	1.00 ± 0.08	1.06 ± 0.04	1.09 ± 0.05
Female						
n	9	10	7	10	10	9
Necropsy body wt	27.5 ± 0.6	26.6 ± 0.7	27.1 ± 1.0	27.0 ± 0.8	25.7 ± 0.7	26.1 ± 0.5
Brain						
Absolute	0.476 ± 0.004	0.475 ± 0.006	0.467 ± 0.006	0.471 ± 0.022	0.464 ± 0.005	0.470 ± 0.006
Relative	17.34 ± 0.41	17.97 ± 0.47	17.34 ± 0.49	17.51 ± 0.78	18.15 ± 0.39	18.05 ± 0.22
Heart						
Absolute	0.152 ± 0.005	0.138 ± 0.005	0.143 ± 0.004	0.142 ± 0.005	0.139 ± 0.006	0.144 ± 0.006
Relative	5.55 ± 0.23	5.19 ± 0.13	5.31 ± 0.20	5.27 ± 0.13	5.41 ± 0.18	5.55 ± 0.25
R. Kidney						
Absolute	0.220 ± 0.010	0.223 ± 0.025[b]	0.213 ± 0.008[c]	0.210 ± 0.007	0.206 ± 0.006	0.204 ± 0.005[d]
Relative	8.01 ± 0.35	8.43 ± 0.78[b]	7.90 ± 0.13[c]	7.79 ± 0.13	8.04 ± 0.20	7.74 ± 0.14[d]
Liver						
Absolute	1.544 ± 0.067	1.540 ± 0.052	1.429 ± 0.071	1.530 ± 0.052	1.400 ± 0.042	1.433 ± 0.053
Relative	56.00 ± 1.78	57.92 ± 1.04	52.72 ± 1.62	56.80 ± 1.12	54.52 ± 0.91	54.91 ± 1.30
Lung						
Absolute	0.195 ± 0.012	0.195 ± 0.018	0.192 ± 0.008	0.213 ± 0.008	0.223 ± 0.009	0.271 ± 0.007**
Relative	7.11 ± 0.44	7.26 ± 0.48	7.08 ± 0.26	7.91 ± 0.22	8.69 ± 0.31**	10.40 ± 0.17**
Thymus						
Absolute	0.046 ± 0.003	0.045 ± 0.004	0.046 ± 0.003	0.043 ± 0.003	0.040 ± 0.002	0.039 ± 0.003
Relative	1.66 ± 0.10	1.67 ± 0.13	1.71 ± 0.12	1.62 ± 0.10	1.57 ± 0.06	1.48 ± 0.10

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9; [c] n=6; [d] n=8

TABLE F7
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 7-Month Interim Evaluation in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
n	5	5	5	5
Male				
Necropsy body wt	35.8 ± 0.7	34.6 ± 0.8	36.2 ± 1.5	34.7 ± 1.1
Brain				
Absolute	0.460 ± 0.008	0.470 ± 0.009	0.458 ± 0.007	0.458 ± 0.011
Relative	12.86 ± 0.06	13.60 ± 0.34	12.72 ± 0.39	13.24 ± 0.31
R. Kidney				
Absolute	0.378 ± 0.012	0.390 ± 0.016	0.410 ± 0.010	0.406 ± 0.012
Relative	10.57 ± 0.31	11.29 ± 0.53	11.40 ± 0.47	11.76 ± 0.49
Liver				
Absolute	1.800 ± 0.046	1.606 ± 0.027*	1.706 ± 0.072	1.810 ± 0.036
Relative	50.30 ± 0.73	46.48 ± 1.25*	47.16 ± 0.69	52.32 ± 0.83
Lung				
Absolute	0.192 ± 0.009	0.208 ± 0.004	0.240 ± 0.010**	0.238 ± 0.006**
Relative	5.37 ± 0.24	6.02 ± 0.20*	6.64 ± 0.11**	6.88 ± 0.16**
Spleen				
Absolute	0.076 ± 0.004	0.078 ± 0.007	0.082 ± 0.004	0.078 ± 0.006
Relative	2.13 ± 0.12	2.26 ± 0.20	2.27 ± 0.09	2.25 ± 0.14
R. Testis				
Absolute	0.122 ± 0.006	0.120 ± 0.003	0.126 ± 0.002	0.126 ± 0.004
Relative	3.42 ± 0.21	3.47 ± 0.11	3.50 ± 0.13	3.64 ± 0.11
Thymus				
Absolute	0.032 ± 0.002	0.043 ± 0.008	0.034 ± 0.005	0.033 ± 0.002
Relative	0.90 ± 0.07	1.23 ± 0.23	0.93 ± 0.12	0.95 ± 0.07
Female				
Necropsy body wt	28.5 ± 1.0	28.5 ± 1.1	28.6 ± 1.4	30.4 ± 0.8
Brain				
Absolute	0.482 ± 0.004	0.470 ± 0.008	0.474 ± 0.010	0.466 ± 0.010
Relative	17.01 ± 0.52	16.58 ± 0.49	16.69 ± 0.79	15.37 ± 0.60
R. Kidney				
Absolute	0.244 ± 0.007	0.250 ± 0.004	0.246 ± 0.007	0.266 ± 0.005*
Relative	8.59 ± 0.14	8.82 ± 0.24	8.63 ± 0.23	8.77 ± 0.33
Liver				
Absolute	1.512 ± 0.037	1.554 ± 0.053	1.416 ± 0.040	1.598 ± 0.038
Relative	53.30 ± 1.71	54.73 ± 1.70	49.69 ± 1.32	52.61 ± 1.38
Lung				
Absolute	0.178 ± 0.010	0.206 ± 0.011	0.228 ± 0.019	0.232 ± 0.022
Relative	6.25 ± 0.24	7.22 ± 0.12	7.94 ± 0.41*	7.62 ± 0.67*
Spleen				
Absolute	0.100 ± 0.005	0.124 ± 0.022	0.098 ± 0.004	0.116 ± 0.009
Relative	3.54 ± 0.24	4.44 ± 0.93	3.45 ± 0.18	3.82 ± 0.32
Thymus				
Absolute	0.044 ± 0.005	0.050 ± 0.004	0.035 ± 0.002	0.040 ± 0.005
Relative	1.55 ± 0.19	1.77 ± 0.19	1.23 ± 0.10	1.31 ± 0.13

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F8
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
n	5	5	5	5
Male				
Necropsy body wt	37.9 ± 1.1	39.0 ± 1.5	41.3 ± 1.7	41.1 ± 1.8
Brain				
Absolute	0.470 ± 0.007	0.472 ± 0.007	0.482 ± 0.004	0.482 ± 0.004
Relative	12.44 ± 0.36	12.16 ± 0.46	11.75 ± 0.43	11.83 ± 0.55
R. Kidney				
Absolute	0.430 ± 0.029	0.410 ± 0.013	0.436 ± 0.024	0.440 ± 0.008
Relative	11.36 ± 0.77	10.55 ± 0.40	10.61 ± 0.64	10.78 ± 0.43
Liver				
Absolute	1.848 ± 0.083[b]	2.114 ± 0.128	2.236 ± 0.307	1.998 ± 0.079
Relative	47.61 ± 2.43[b]	54.47 ± 3.90	54.41 ± 7.79	48.72 ± 0.64
Lung				
Absolute	0.234 ± 0.017	0.246 ± 0.021	0.306 ± 0.020*	0.382 ± 0.019**
Relative	6.24 ± 0.65	6.28 ± 0.34	7.44 ± 0.48	9.44 ± 0.86**
Spleen				
Absolute	0.130 ± 0.041	0.078 ± 0.008	0.096 ± 0.019	0.074 ± 0.006
Relative	3.57 ± 1.26	2.00 ± 0.20	2.34 ± 0.48	1.82 ± 0.18
Thymus				
Absolute	0.054 ± 0.007	0.047 ± 0.005	0.046 ± 0.008	0.049 ± 0.007
Relative	1.44 ± 0.23	1.19 ± 0.09	1.14 ± 0.23	1.19 ± 0.17
Female				
Necropsy body wt	39.5 ± 3.2	37.1 ± 1.6	38.3 ± 1.9	34.4 ± 2.1
Brain				
Absolute	0.498 ± 0.005	0.496 ± 0.004	0.488 ± 0.004	0.500 ± 0.014
Relative	12.89 ± 0.90	13.47 ± 0.57	12.85 ± 0.62	14.70 ± 0.75
R. Kidney				
Absolute	0.296 ± 0.014	0.306 ± 0.009	0.308 ± 0.023	0.272 ± 0.007
Relative	7.71 ± 0.78	8.29 ± 0.29	8.14 ± 0.80	8.05 ± 0.64
Liver				
Absolute	1.898 ± 0.093	1.810 ± 0.030	1.896 ± 0.090	1.770 ± 0.056
Relative	48.99 ± 3.84	49.05 ± 1.72	49.79 ± 2.81	52.07 ± 2.93
Lung				
Absolute	0.248 ± 0.010	0.264 ± 0.010	0.294 ± 0.018	0.340 ± 0.026**
Relative	6.37 ± 0.30	7.12 ± 0.04	7.70 ± 0.43	10.07 ± 1.02**
Spleen				
Absolute	0.124 ± 0.018	0.130 ± 0.006[b]	0.130 ± 0.011	0.118 ± 0.011
Relative	3.27 ± 0.63	3.46 ± 0.27[b]	3.42 ± 0.34	3.47 ± 0.39
Thymus				
Absolute	0.048 ± 0.004	0.056 ± 0.005	0.066 ± 0.007	0.052 ± 0.006
Relative	1.23 ± 0.06	1.52 ± 0.15	1.73 ± 0.19	1.55 ± 0.25

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=4

APPENDIX G
HEMATOLOGY RESULTS

TABLE G1
Hematology Data for Rats in the 13-Week Inhalation Study of Nickel Oxide[a]

	0 mg/m^3	0.6 mg/m^3	1.2 mg/m^3	2.5 mg/m^3	5 mg/m^3	10 mg/m^3
Male						
n	9	10	10	9	10	10
Hematocrit (%)	43.6 ± 0.5	43.3 ± 0.2	44.2 ± 0.5	43.8 ± 0.8	43.8 ± 0.7	46.4 ± 0.5**
Hemoglobin (g/dL)	15.3 ± 0.2	15.4 ± 0.1	15.5 ± 0.2	15.7 ± 0.3	15.6 ± 0.2	16.6 ± 0.2**
Erythrocytes ($10^6/\mu L$)	8.33 ± 0.08	8.42 ± 0.03	8.46 ± 0.14	8.51 ± 0.15	8.55 ± 0.12	9.02 ± 0.11**
Mean cell volume (fL)	53.0 ± 0.2	52.2 ± 0.2	53.0 ± 0.6	52.2 ± 0.2	51.9 ± 0.3**	52.2 ± 0.3
Mean cell hemoglobin concentration (g/dL)	35.1 ± 0.2	35.6 ± 0.2	35.1 ± 0.2	35.9 ± 0.1**	35.7 ± 0.1	35.7 ± 0.2
Reticulocytes ($10^6/\mu L$)	0.5 ± 0.1	0.6 ± 0.1	0.9 ± 0.1*	0.7 ± 0.1	0.6 ± 0.1	0.5 ± 0.1
Leukocytes ($10^3/\mu L$)	2.22 ± 0.24	2.48 ± 0.23	3.56 ± 0.40*	2.67 ± 0.30	3.00 ± 0.37	3.34 ± 0.31*
Segmented neutrophils ($10^3/\mu L$)	0.62 ± 0.07	0.71 ± 0.09	1.01 ± 0.08**	1.06 ± 0.15*	1.14 ± 0.18*	1.26 ± 0.18**
Lymphocytes ($10^3/\mu L$)	1.55 ± 0.19	1.71 ± 0.15	2.48 ± 0.31	1.56 ± 0.16	1.79 ± 0.24	1.98 ± 0.23
Monocytes ($10^3/\mu L$)	0.04 ± 0.02	0.05 ± 0.01	0.06 ± 0.03	0.03 ± 0.01	0.04 ± 0.02	0.08 ± 0.02
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.03 ± 0.01	0.05 ± 0.02	0.13 ± 0.04	0.13 ± 0.04	0.20 ± 0.05*	0.12 ± 0.04

TABLE G1
Hematology Data for Rats in the 13-Week Inhalation Study of Nickel Oxide (continued)

	0 mg/m^3	0.6 mg/m^3	1.2 mg/m^3	2.5 mg/m^3	5 mg/m^3	10 mg/m^3
Female						
n	10	10	10	10	10	10
Hematocrit (%)	40.8 ± 1.0	43.5 ± 1.0	42.7 ± 0.3*	42.5 ± 1.0**	43.3 ± 0.2**	44.0 ± 0.5**
Hemoglobin (g/dL)	14.4 ± 0.3	15.6 ± 0.4**	15.3 ± 0.1**	15.3 ± 0.4**	15.7 ± 0.1**	15.9 ± 0.1**
Erythrocytes ($10^6/\mu L$)	7.2 ± 0.2	7.8 ± 0.2	7.7 ± 0.1	7.7 ± 0.2*	7.9 ± 0.0**	8.0 ± 0.1**
Mean cell volume (fL)	57.3 ± 0.5	56.7 ± 0.2	56.2 ± 0.2*	56.3 ± 0.2*	56.1 ± 0.3*	56.0 ± 0.3*
Mean cell hemoglobin concentration (g/dL)	35.3 ± 0.1	35.9 ± 0.1**	35.9 ± 0.1**	36.0 ± 0.1**	36.2 ± 0.3**	36.2 ± 0.2**
Reticulocytes ($10^6/\mu L$)	0.4 ± 0.0	0.3 ± 0.0	0.4 ± 0.0	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
Leukocytes ($10^3/\mu L$)	2.04 ± 0.18	2.40 ± 0.15	2.64 ± 0.15*	3.50 ± 0.18**	2.89 ± 0.24**	3.55 ± 0.21**
Segmented neutrophils ($10^3/\mu L$)	0.45 ± 0.06	0.73 ± 0.08*	0.79 ± 0.07**	0.91 ± 0.10**	0.74 ± 0.09**	0.92 ± 0.09**
Lymphocytes ($10^3/\mu L$)	1.55 ± 0.16	1.63 ± 0.11	1.80 ± 0.15	2.48 ± 0.13**	2.09 ± 0.17**	2.53 ± 0.17**
Monocytes ($10^3/\mu L$)	0.02 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.06 ± 0.01**	0.05 ± 0.01*	0.09 ± 0.02**
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.01 ± 0.01	0.03 ± 0.01	0.04 ± 0.01	0.02 ± 0.01	0.01 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.02 ± 0.01	0.11 ± 0.03*	0.18 ± 0.03**	0.12 ± 0.03**	0.18 ± 0.03**	0.23 ± 0.05**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error

TABLE G2
Hematology Data for Rats at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m^3	0.62 mg/m^3	1.25 mg/m^3	2.5 mg/m^3
n	5	5	5	5
Male				
Hematocrit (%)	48.3 ± 0.4	48.4 ± 1.5	49.1 ± 0.8	47.1 ± 4.7
Hemoglobin (g/dL)	16.3 ± 0.2	16.2 ± 0.5	16.6 ± 0.2	15.9 ± 1.7
Erythrocytes ($10^6/\mu L$)	8.75 ± 0.07	8.66 ± 0.26	8.92 ± 0.11	8.68 ± 0.73
Mean cell volume (fL)	54.8 ± 0.4	55.2 ± 0.7	54.6 ± 0.2	53.6 ± 1.2
Mean cell hemoglobin (pg)	18.6 ± 0.1	18.7 ± 0.3	18.6 ± 0.1	18.2 ± 0.5
Mean cell hemoglobin concentration (g/dL)	33.7 ± 0.4	33.4 ± 0.1	33.7 ± 0.3	33.7 ± 0.4
Reticulocytes ($10^6/\mu L$)	0.3 ± 0.0	0.1 ± 0.0*	0.2 ± 0.0*	0.3 ± 0.1
Leukocytes ($10^3/\mu L$)	5.68 ± 0.54	5.60 ± 0.26	6.08 ± 0.48	7.44 ± 0.68
Segmented neutrophils ($10^3/\mu L$)	1.84 ± 0.22	1.64 ± 0.32	2.00 ± 0.21	2.54 ± 0.45
Lymphocytes ($10^3/\mu L$)	3.46 ± 0.27	3.56 ± 0.25	3.48 ± 0.27	4.54 ± 0.48
Monocytes ($10^3/\mu L$)	0.38 ± 0.08	0.36 ± 0.02	0.50 ± 0.16	0.34 ± 0.04
Eosinophils ($10^3/\mu L$)	0.06 ± 0.02	0.06 ± 0.04	0.06 ± 0.02	0.06 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.02 ± 0.01	0.02 ± 0.01	0.04 ± 0.04
Female				
Hematocrit (%)	47.4 ± 1.4	47.2 ± 0.7	47.8 ± 0.9	49.4 ± 0.9
Hemoglobin (g/dL)	16.4 ± 0.2	16.2 ± 0.3	16.4 ± 0.3	17.1 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.11 ± 0.18	7.83 ± 0.15	7.96 ± 0.17	8.22 ± 0.16
Mean cell volume (fL)	58.0 ± 0.3	60.0 ± 0.5*	59.6 ± 0.6	59.6 ± 0.5
Mean cell hemoglobin (pg)	20.3 ± 0.3	20.7 ± 0.2	20.7 ± 0.1	20.8 ± 0.2
Mean cell hemoglobin concentration (g/dL)	34.7 ± 0.8	34.4 ± 0.3	34.4 ± 0.3	34.6 ± 0.3
Reticulocytes ($10^6/\mu L$)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Leukocytes ($10^3/\mu L$)	4.84 ± 0.29	4.92 ± 0.39	4.20 ± 0.33	4.60 ± 0.32
Segmented neutrophils ($10^3/\mu L$)	1.22 ± 0.21	1.06 ± 0.14	1.12 ± 0.10	1.14 ± 0.20
Lymphocytes ($10^3/\mu L$)	3.26 ± 0.28	3.68 ± 0.31	2.72 ± 0.26	3.20 ± 0.22
Monocytes ($10^3/\mu L$)	0.30 ± 0.03	0.16 ± 0.04	0.28 ± 0.07	0.24 ± 0.08
Eosinophils ($10^3/\mu L$)	0.08 ± 0.04	0.04 ± 0.02	0.08 ± 0.04	0.00 ± 0.00
Nucleated erythrocytes ($10^3/\mu L$)	0.02 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.03 ± 0.02

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error

TABLE G3
Hematology Data for Mice in the 13-Week Inhalation Study of Nickel Oxide[a]

	0 mg/m^3	0.6 mg/m^3	1.2 mg/m^3	2.5 mg/m^3	5 mg/m^3	10 mg/m^3
Male						
n	5	5	5	5	5	5
Hematocrit (%)	44.4 ± 2.0	42.0 ± 0.8	43.3 ± 1.3	42.5 ± 0.6	44.3 ± 0.7	42.4 ± 1.5
Hemoglobin (g/dL)	14.6 ± 0.3	14.3 ± 0.4	14.9 ± 0.5	14.8 ± 0.2	15.1 ± 0.3	14.5 ± 0.5
Erythrocytes ($10^6/\mu L$)	8.70 ± 0.31	8.31 ± 0.15	8.46 ± 0.31	7.96 ± 0.23	8.65 ± 0.08	8.37 ± 0.25
Mean cell volume (fL)	51.8 ± 0.7	51.6 ± 0.9	52.0 ± 0.5	54.2 ± 1.4	52.0 ± 0.3	51.2 ± 0.5
Mean cell hemoglobin concentration (g/dL)	33.0 ± 0.9	33.9 ± 0.9	34.3 ± 0.3	34.8 ± 0.2*	34.2 ± 0.1	34.3 ± 0.3
Reticulocytes ($10^6/\mu L$)	0.4 ± 0.1	0.7 ± 0.3	0.5 ± 0.1	0.5 ± 0.2	0.4 ± 0.0	0.5 ± 0.1
Leukocytes ($10^3/\mu L$)	1.24 ± 0.53	1.50 ± 0.60	1.60 ± 0.46	1.34 ± 0.19	0.98 ± 0.21	1.76 ± 0.30
Segmented neutrophils ($10^3/\mu L$)	0.81 ± 0.41	0.62 ± 0.24	0.50 ± 0.14	0.59 ± 0.10	0.32 ± 0.06	0.48 ± 0.12
Lymphocytes ($10^3/\mu L$)	0.41 ± 0.14	0.87 ± 0.43	1.07 ± 0.32	0.74 ± 0.15	0.64 ± 0.17	1.24 ± 0.24*
Monocytes ($10^3/\mu L$)	0.02 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.00	0.02 ± 0.01	0.03 ± 0.01
Eosinophils ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.01 ± 0.01	0.06 ± 0.04	0.09 ± 0.03	0.03 ± 0.02	0.07 ± 0.02	0.09 ± 0.03

TABLE G3
Hematology Data for Mice in the 13-Week Inhalation Study of Nickel Oxide (continued)

	0 mg/m^3	0.6 mg/m^3	1.2 mg/m^3	2.5 mg/m^3	5 mg/m^3	10 mg/m^3
Female						
n	4	5	2	5	5	5
Hematocrit (%)	40.7 ± 0.5	39.8 ± 0.9	42.5 ± 0.8	41.8 ± 0.6	42.4 ± 0.3*	42.5 ± 0.3*
Hemoglobin (g/dL)	14.2 ± 0.1	14.1 ± 0.4	14.9 ± 0.1	14.7 ± 0.2	15.0 ± 0.1**	14.7 ± 0.1
Erythrocytes ($10^6/\mu L$)	8.10 ± 0.06	7.91 ± 0.17	8.38 ± 0.07	8.30 ± 0.11	8.48 ± 0.08*	8.50 ± 0.07*
Mean cell volume (fL)	51.0 ± 0.4	51.2 ± 0.2	51.5 ± 1.5	51.0 ± 0.0	50.6 ± 0.2	50.4 ± 0.4
Mean cell hemoglobin concentration (g/dL)	35.0 ± 0.2	35.5 ± 0.3	35.0 ± 0.7	35.2 ± 0.1	35.3 ± 0.2	34.7 ± 0.1
Reticulocytes ($10^6/\mu L$)	0.5 ± 0.1	0.5 ± 0.1	1.2 ± 0.2	0.6 ± 0.1	0.5 ± 0.1	0.7 ± 0.2
Leukocytes ($10^3/\mu L$)	1.03 ± 0.09	0.92 ± 0.19	3.10 ± 0.00	0.68 ± 0.12	1.34 ± 0.11	1.18 ± 0.42
Segmented neutrophils ($10^3/\mu L$)	0.39 ± 0.09	0.37 ± 0.11	1.01 ± 0.14	0.23 ± 0.04	0.42 ± 0.10	0.43 ± 0.15
Lymphocytes ($10^3/\mu L$)	0.62 ± 0.06	0.52 ± 0.10	2.06 ± 0.11	0.42 ± 0.10	0.92 ± 0.10	0.73 ± 0.28
Monocytes ($10^3/\mu L$)	0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.03	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.01	0.00 ± 0.00	0.01 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01	0.19 ± 0.09	0.01 ± 0.00	0.06 ± 0.01	0.02 ± 0.01

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error

TABLE G4
Hematology Data for Mice at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m^3	1.25 mg/m^3	2.5 mg/m^3	5 mg/m^3
Male				
n	5	5	5	5
Hematocrit (%)	51.6 ± 5.5	48.0 ± 1.3	50.6 ± 4.5	46.5 ± 0.5
Hemoglobin (g/dL)	17.0 ± 1.7	15.9 ± 0.4	16.9 ± 1.6	15.4 ± 0.1
Erythrocytes ($10^6/\mu L$)	10.40 ± 1.36	9.41 ± 0.34	10.03 ± 0.91	9.08 ± 0.14
Mean cell volume (fL)	49.8 ± 1.0	50.8 ± 0.7	50.0 ± 0.0	51.0 ± 0.6
Mean cell hemoglobin (pg)	16.6 ± 0.4	16.9 ± 0.3	16.8 ± 0.2	17.0 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.0 ± 0.3	33.2 ± 0.1	33.3 ± 0.4	33.1 ± 0.2
Reticulocytes ($10^6/\mu L$)	0.3 ± 0.0[b]	0.1 ± 0.0	0.2 ± 0.0[b]	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	3.44 ± 0.51	4.08 ± 0.60	2.28 ± 0.16	4.08 ± 0.19
Segmented neutrophils ($10^3/\mu L$)	1.16 ± 0.31	1.72 ± 0.25	0.84 ± 0.14	1.50 ± 0.23
Lymphocytes ($10^3/\mu L$)	2.08 ± 0.22	2.20 ± 0.41	1.36 ± 0.16	2.34 ± 0.27
Monocytes ($10^3/\mu L$)	0.18 ± 0.13	0.14 ± 0.07	0.04 ± 0.02	0.16 ± 0.07
Eosinophils ($10^3/\mu L$)	0.04 ± 0.02	0.00 ± 0.00	0.06 ± 0.02	0.08 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01
Female				
n	4	5	4	5
Hematocrit (%)	45.5 ± 0.5	46.2 ± 0.5	46.7 ± 0.4	47.2 ± 0.9
Hemoglobin (g/dL)	15.5 ± 0.1	15.6 ± 0.2	15.7 ± 0.1	16.0 ± 0.3
Erythrocytes ($10^6/\mu L$)	9.17 ± 0.12	9.23 ± 0.12	9.44 ± 0.03	9.40 ± 0.16
Mean cell volume (fL)	49.3 ± 0.5	49.6 ± 0.2	49.0 ± 0.4	49.8 ± 0.5
Mean cell hemoglobin (pg)	16.9 ± 0.2	17.0 ± 0.2	16.6 ± 0.2	17.0 ± 0.1
Mean cell hemoglobin concentration (g/dL)	34.1 ± 0.1	33.8 ± 0.2	33.6 ± 0.1	33.9 ± 0.1
Reticulocytes ($10^6/\mu L$)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Leukocytes ($10^3/\mu L$)	2.45 ± 0.33	2.65 ± 0.21[b]	2.70 ± 0.26	2.36 ± 0.29
Segmented neutrophils ($10^3/\mu L$)	1.03 ± 0.40	0.90 ± 0.19[b]	1.15 ± 0.05	0.70 ± 0.13
Lymphocytes ($10^3/\mu L$)	1.33 ± 0.23	1.68 ± 0.10[b]	1.38 ± 0.18	1.54 ± 0.19
Monocytes ($10^3/\mu L$)	0.08 ± 0.03	0.08 ± 0.03[b]	0.08 ± 0.03	0.08 ± 0.02
Eosinophils ($10^3/\mu L$)	0.03 ± 0.03	0.00 ± 0.00[b]	0.05 ± 0.03	0.02 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01

[a] Mean ± standard error
[b] n=4

APPENDIX H
TISSUE BURDEN IN RATS

TABLE H1
Lung Weight and Lung Burden in Rats in the 16-Day Inhalation Study of Nickel Oxide[a]

	0 mg/m³	1.2 mg/m³	5 mg/m³	10 mg/m³
n	5	5	5	5
Male				
Absolute lung wt (g)	0.856 ± 0.047	0.870 ± 0.046	0.822 ± 0.041	1.068 ± 0.056*
μg Ni/lung	—[b]	36 ± 1.3**	88 ± 4.8**	284 ± 9.7**
μg Ni/g lung	—	42 ± 2.8**	108 ± 4.3**	267 ± 12.3**
μg Ni/g control lung	—	42 ± 1.6**	103 ± 5.6**	331 ± 11.4**
Female				
Absolute lung wt (g)	0.739 ± 0.028	0.704 ± 0.017	0.731 ± 0.040	0.861 ± 0.025*
μg Ni/lung	—	38 ± 4.8**	88 ± 3.3**	293 ± 13.4**
μg Ni/g lung	—	54 ± 5.7**	122 ± 10.3**	340 ± 10.4**
μg Ni/g control lung	—	52 ± 6.5**	119 ± 4.5**	396 ± 18.2**

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test (lung weight) or Shirley's test (lung burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error
[b] Results were below 0.182 μg Ni (the limit of detection), or below the level of quantitation.

TABLE H2
Kidney Weight and Kidney Burden in Rats in the 16-Day Inhalation Study of Nickel Oxide[a]

	0 mg/m³	10 mg/m³
n	5	5
Male		
Absolute kidney wt (g)	1.76 ± 0.05	1.71 ± 0.02
μg Ni/kidney	—[b]	—
μg Ni/g kidney	—	—
Female		
Absolute kidney wt (g)	1.25 ± 0.01	1.71 ± 0.02**
μg Ni/kidney	—	—
μg Ni/g kidney	—	—

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test (kidney weight) or Shirley's test (kidney burden parameters)
[a] Mean ± standard error
[b] Results were below 0.182 μg Ni (the limit of detection), or below the level of quantitation.

TABLE H3
Lung Weight and Lung Burden in Male Rats in the 13-Week Inhalation Study of Nickel Oxide[a]

	0 mg/m³	0.6 mg/m³	2.5 mg/m³	10 mg/m³
n	6	6	6	6
4 weeks				
μg Ni/g lung	—[b]	33 ± 2.3**	110 ± 6.6**	263 ± 18.5**
9 weeks				
μg Ni/g lung	—	53 ± 6.8**	143 ± 27.9**	400 ± 31.2**
13 weeks				
Absolute lung wt (g)	0.954 ± 0.043	1.082 ± 0.028	1.534 ± 0.032**	2.108 ± 0.097**
μg Ni/lung	—	86 ± 6.0**	276 ± 34.6**	1,092 ± 63.1**
μg Ni/g lung	—	80 ± 5.5**	181 ± 25.6**	524 ± 38.2**
μg Ni/g control lung	—	91 ± 6.3**	289 ± 36.3**	1,146 ± 66.2**

** Significantly different ($P \leq 0.01$) from the control group by Williams' test (lung weight) or Shirley's test (lung burden parameters)
[a] Mean ± standard error
[b] Results were below 0.301 μg Ni (the limit of detection), or below the level of quantitation.

TABLE H4
Lung Weight and Lung Burden in Rats in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m³	0.62 mg/m³	1.25 mg/m³	2.5 mg/m³
Male				
n	6	7	7	7
7-Month interim evaluation				
Absolute lung wt (g)	1.72 ± 0.07	1.85 ± 0.07	2.43 ± 0.11**	2.59 ± 0.06**
μg Ni/lung	—[b]	326 ± 29.6**	930 ± 21.3**	1,817 ± 68.6**
μg Ni/g lung	—	175 ± 10.6**	388 ± 18.7**	701 ± 24.1**
μg Ni/g control lung	—	189 ± 17.2**	541 ± 12.4**	1,057 ± 39.9**
n	5	5	5	5
15-Month interim evaluation				
Absolute lung wt (g)	2.20 ± 0.04	2.15 ± 0.10	3.30 ± 0.16**	4.09 ± 0.12**
μg Ni/lung	—	696 ± 41.6**	2,439 ± 71.9**	4,573 ± 485.4**
μg Ni/g lung	—	328 ± 30.2**	746 ± 46.6**	1,116 ± 108.2**
μg Ni/g control lung	—	317 ± 18.9**	1,110 ± 32.7**	2,082 ± 221.1**
Female				
n	7	7	7	6
7-Month interim evaluation				
Absolute lung wt (g)	1.14 ± 0.03	1.31 ± 0.03*	1.65 ± 0.07**	1.78 ± 0.08**
μg Ni/lung	—	226 ± 13.3**	792 ± 86.5**	1,279 ± 132.2**
μg Ni/g lung	—	173 ± 10.1**	477 ± 44.4**	713 ± 45.2**
μg Ni/g control lung	—	198 ± 11.7**	694 ± 75.8**	1,122 ± 115.9**
n	5	5	5	5
15-Month interim evaluation				
Absolute lung wt (g)	1.56 ± 0.11	1.79 ± 0.10	2.41 ± 0.11**	3.02 ± 0.13**
μg Ni/lung	—	471 ± 42.5**	1,703 ± 140.5**	2,810 ± 389.1**
μg Ni/g lung	—	262 ± 14.8**	706 ± 41.8**	949 ± 146.4**
μg Ni/g control lung	—	302 ± 27.3**	1,093 ± 90.2**	1,804 ± 249.7**

* Significantly different ($P \leq 0.05$) from the control group by Williams' test (lung weight) or Shirley's test (lung burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error
[b] Results were below 0.540 μg Ni (the limit of detection) for 7-month males, 0.660 μg Ni for 7-month females, or 0.450 μg Ni for 15-month males and females, or below the level of quantitation.

APPENDIX I
TISSUE BURDEN IN MICE

TABLE I1
Lung Weight and Lung Burden in Mice in the 16-Day Inhalation Study of Nickel Oxide[a]

	0 mg/m³	1.2 mg/m³	2.5 mg/m³	5 mg/m³
n	5	5	5	5
Male				
Absolute lung weight (g)	0.159 ± 0.005	0.154 ± 0.009	0.156 ± 0.003	0.156 ± 0.010
μg Ni/lung	—[b]	5 ± 0.1**	7 ± 0.5**	13 ± 0.7**
μg Ni/g lung	—	32 ± 2.4**	46 ± 3.6**	84 ± 7.8**
μg Ni/g control lung	—	31 ± 0.8**	45 ± 3.1**	81 ± 4.5**
Female				
Absolute lung weight (g)	0.149 ± 0.006	0.133 ± 0.004	0.141 ± 0.006	0.168 ± 0.006
μg Ni/lung	—	4 ± 0.2**	6 ± 0.4**	12 ± 0.8**
μg Ni/g lung	—	31 ± 2.1**	43 ± 0.9**	71 ± 5.7**
μg Ni/g control lung	—	27 ± 1.3**	41 ± 2.5**	80 ± 5.7**

** Significantly different ($P \leq 0.01$) from the control group by Dunnett's test (lung weight) or Shirley's test (lung burden parameters)
[a] Mean ± standard error
[b] Results were below 0.213 μg Ni (the limit of detection), or below the level of quantitation.

TABLE I2
Lung Weight and Lung Burden in Male Mice in the 13-Week Inhalation Study of Nickel Oxide[a]

	0 mg/m³	0.6 mg/m³	2.5 mg/m³	10 mg/m³
Male				
n	6	5	6	5
Absolute lung weight (g)	0.176 ± 0.012	0.179 ± 0.004	0.179 ± 0.014	0.244 ± 0.019**
μg Ni/lung	—[b]	7 ± 0.6**	36 ± 3.3**	171 ± 15.5**
μg Ni/g lung	—	42 ± 2.9**	202 ± 18.3**	736 ± 123.0**
μg Ni/g control lung	—	42 ± 3.4**	204 ± 18.9**	973 ± 88.0**

** Significantly different ($P \leq 0.01$) from the control group by Dunnett's test (lung weight) or Shirley's test (lung burden parameters)
[a] Mean ± standard error
[b] Results were below 0.255 μg Ni (the limit of detection), or below the level of quantitation.

TABLE I3
Lung Weight and Lung Burden in Mice in the 2-Year Inhalation Study of Nickel Oxide[a]

	0 mg/m³	1.25 mg/m³	2.5 mg/m³	5 mg/m³
n	5	5	5	5
Male				
7-Month interim evaluation				
Absolute lung weight (g)	0.192 ± 0.009	0.208 ± 0.004	0.240 ± 0.010**	0.238 ± 0.006**
μg Ni/lung	—[b]	34 ± 2.1**	107 ± 12.0**	246 ± 11.2**
μg Ni/g lung	—	162 ± 9.6**	442 ± 37.1**	1,034 ± 33.1**
μg Ni/g control lung	—	176 ± 11.0**	556 ± 62.3**	1,283 ± 58.1**
15-Month interim evaluation				
Absolute lung weight (g)	0.234 ± 0.017	0.246 ± 0.021	0.306 ± 0.020*	0.382 ± 0.019**
μg Ni/lung	—	80 ± 5.1**	296 ± 35.5**	696 ± 81.9**
μg Ni/g lung	—	331 ± 30.3**	959 ± 67.1**	1,798 ± 134.5**
μg Ni/g control lung	—	340 ± 21.8**	1,265 ± 151.5**	2,973 ± 349.9**
Female				
7-Month interim evaluation				
Absolute lung weight (g)	0.178 ± 0.010	0.206 ± 0.011	0.228 ± 0.019	0.232 ± 0.022
μg Ni/lung	—	35 ± 1.6**	120 ± 8.1**	196 ± 15.3**
μg Ni/g lung	—	169 ± 6.0**	533 ± 36.4**	861 ± 70.1**
μg Ni/g control lung	—	195 ± 9.1**	674 ± 45.2**	1,101 ± 86.2**
15-Month interim evaluation				
Absolute lung weight (g)	0.248 ± 0.010	0.264 ± 0.010	0.294 ± 0.018	0.340 ± 0 026**
μg Ni/lung	—	119 ± 10.1**	365 ± 39.9**	771 ± 111.9**
μg Ni/g lung	—	451 ± 31.4**	1,237 ± 102.6**	2,258 ± 265.1**
μg Ni/g control lung	—	481 ± 40.9**	1,472 ± 160.9**	3,108 ± 451.3**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's (lung weight) or Shirley's tests (lung burden parameters)
** $P \leq 0.01$
[a] Mean ± standard error
[b] Results were below 0.400 μg Ni (the limit of detection) for 7-month mice or 0.352 μg Ni for 15-month mice, or below the level of quantitation.

APPENDIX J
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE J1
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 13-Week Inhalation Study of Nickel Oxide[a]

	0 mg/m^3	2.5 mg/m^3	5 mg/m^3	10 mg/m^3
Male				
n	10	9	10	10
Weights (g)				
Right cauda	0.136 ± 0.006	0.137 ± 0.005	0.138 ± 0.005	0.145 ± 0.004
Right epididymis	0.516 ± 0.015	0.487 ± 0.011	0.505 ± 0.008	0.505 ± 0.012
Right testis	1.340 ± 0.028	1.438 ± 0.037	1.418 ± 0.034	1.455 ± 0.054
Epididymal spermatozoal measurements				
Motility (%)	95.27 ± 0.51	94.61 ± 0.63	94.45 ± 0.38	94.03 ± 0.47
Abnormality (%)	0.680 ± 0.080	0.822 ± 0.127	0.940 ± 0.043	0.880 ± 0.061
Concentration (10^6/g cauda epididymal tissue)	949 ± 56	874 ± 65	819 ± 53	754 ± 24**
Female[b]				
n	10	9[c]	10	8[d]
Estrous cycle length (days)	4.80 ± 0.25	4.67 ± 0.17	4.60 ± 0.16	4.75 ± 0.25
Estrous stages (% of cycle)				
Diestrus	32.9	34.3	32.9	34.3
Proestrus	8.6	12.9	12.9	14.3
Estrus	30.0	31.4	35.7	34.3
Metestrus	20.0	15.7	18.6	15.7
Unclear diagnosis	8.6	5.7	0.0	1.4

** Significantly different ($P \leq 0.01$) from the control group by Shirley's test
[a] Data are presented as mean ± standard error.
[b] There is no evidence of any differences between the exposed and control groups in cycle length or in relative length of time spent in estrous stages.
[c] Estrous cycle was longer than 7 days or was unclear in 1 of 10 animals.
[d] Estrous cycle was longer than 7 days or was unclear in 2 of 10 animals.

TABLE J2
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 13-Week Inhalation Study of Nickel Oxide[a]

	0 mg/m^3	2.5 mg/m^3	5 mg/m^3	10 mg/m^3
Male				
n	10	10	10	9
Weights (g)				
Right cauda	0.010 ± 0.001	0.008 ± 0.001	0.010 ± 0.001	0.010 ± 0.001
Right epididymis	0.062 ± 0.003	0.056 ± 0.004	0.063 ± 0.004	0.056 ± 0.004
Right testis	0.121 ± 0.005	0.112 ± 0.004	0.123 ± 0.004	0.106 ± 0.009
Epididymal spermatozoal measurements				
Motility (%)	95.40 ± 0.30	95.40 ± 0.25	95.50 ± 0.29	95.68 ± 0.28
Abnormality (%)	1.70 ± 0.15	1.34 ± 0.13	1.62 ± 0.19	2.40 ± 1.06
Concentration (10^6/g cauda epididymal tissue)	1,714 ± 210	1,616 ± 262	1,815 ± 190	1,735 ± 204
Female[b]				
n	9	10	9[c]	9
Estrous cycle length (days)	4.11 ± 0.11	4.30 ± 0.21	4.00 ± 0.17	4.11 ± 0.11
Estrous stages (% of cycle)				
Diestrus	31.7	25.7	31.4	31.7
Proestrus	19.0	11.4	14.3	23.8
Estrus	27.0	38.6	34.3	22.2
Metestrus	20.6	22.9	20.0	22.2
Unclear diagnosis	1.6	1.4	0.0	0.0

[a] Data are presented as mean ± standard error. Differences from the control group for all study parameters are not significant by Dunn's or Dunnett's tests.
[b] There is no evidence of any differences between the exposed and control groups in cycle length or in relative length of time spent in estrous stages.
[c] Estrous cycle was longer than 7 days or was unclear in 1 of 10 animals.

APPENDIX K
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF NICKEL OXIDE

Nickel oxide, which was manufactured by the Societe Metallurgique le Nickel (Paris, France), was generously supplied by International Nickel Company, Ltd., (Toronto, Ontario) in one lot (I042983), which was used during the 16-day, 13-week, and 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the nickel oxide studies are on file at the National Institute of Environmental Health Sciences.

The chemical, an olive gray powder, was identified as high temperature (sintered) nickel oxide by elemental, melting point, and solubility analyses. The chemical had a melting point of greater than 300° C and was not soluble in boiling concentrated nitric acid or concentrated sulfuric acid. Elemental analysis for nickel was in agreement with the theoretical value for nickel oxide. The melting point and solubility characteristics were consistent with those expected for high temperature (sintered) nickel oxide (Weast, 1976; Rhoda *et al.*, 1981).

The purity of lot I042983 was determined by elemental analysis, weight loss on drying, and spark source mass spectrometry. A sample of lot I042983 was also analyzed by Truesdail Laboratories (Tustin, CA) for five elements to determine if it met American Society of Testing and Materials (ASTM) specifications.

Elemental analysis for nickel (78.8%) was in agreement with the theoretical value for nickel oxide. Weight loss on drying indicated less than 0.05% water. Spark source mass spectrometry indicated total impurities less than or equal to 3,500 ppm; the major inorganic impurities were cobalt (approximately 2,200 ppm), iron (670 ppm), and sulfur (200 ppm). Analyses for nickel, cobalt, copper, iron, and sulfur indicated conformance with ASTM specifications for Grade 75 nickel oxide sinter (ASTM, 1974). The overall purity was determined to be greater than 99%.

No accelerated chemical stability studies were performed for nickel oxide based on literature information about the physical and chemical properties of the compound (*Kirk-Othmer*, 1978). The melting point and oxidation state indicate that nickel oxide should be thermally stable at temperatures up to 340° C when protected from light (Larkins, 1967; Weast, 1976). To ensure stability, the analytical chemistry laboratory recommended that the bulk chemical be stored protected from light at room temperature.

The bulk chemical was stored in amber glass bottles at room temperature. Periodic monitoring of the bulk chemical was performed by Huffman Laboratories, Inc., (Golden, CO) prior to all studies, once during the 16-day and 13-week studies and every 3 to 5 months during the 2-year studies by elemental analysis for nickel and weight loss on drying. On three occasions out of 20 analyses, the values for nickel in the samples fell outside the range recommended by the analytical chemistry laboratory. Occasionally, the weight loss on drying exceeded the specification of 0.1%. Because the excursions from specification were sporadic and occurred in the bulk and reference samples, it was concluded that there was no degradation of the bulk chemical during the studies.

AEROSOL GENERATION AND EXPOSURE SYSTEM

Nickel oxide aerosol was generated from 4-inch (16-day and 13-week studies) or 2-inch (2-year studies) fluid bed generators (FBGs). Figure K1 shows the schematic of the FBG with the gravity feed and catch

pan collection systems. The FBG contained a bed of stainless steel powder of a diameter too heavy to be carried from the generator in the flow of air. The nickel oxide was added to the stainless steel bed, and the motion of the bed when air was passed through the FBG released the much smaller nickel oxide particles into the air. A Kr-85 discharger was placed in the generator to reduce the electrical charge on the aerosol. The nickel oxide aerosol was mixed with diluting air to achieve the desired concentrations and was delivered to the exposure chambers. Fresh nickel oxide-containing bed material was constantly added to the generator from a hopper located above the generator; the nickel oxide-depleted stainless steel powder was continually drained from the FBG through an overflow port located at the side of the generator. The depleted stainless steel bed material, collected in an enclosed container at the base of the generator, was loaded into a V-tube mixer and was mixed with a sufficient amount of nickel oxide to replenish the bed and maintain a stable aerosol concentration. The amount of nickel oxide added to each bed depended on the aerosol concentration desired. The aerosol generation assembly was enclosed in a walk-in hood. Air was circulated through HEPA filters to remove suspended particles in the enclosure. The aerosol delivery system is shown in Figure K2.

Stainless steel, multi-tiered, whole-body exposure chambers (H1000 and H2000, Hazleton Systems, Aberdeen, MD) were used to expose the rats and mice in these studies (Figure K3). In the 16-day studies, the H2000 chambers were used for the 1.2, 2.5, and 10 mg/m^3 groups, and the H1000 chambers were used for the 0, 5, and 30 mg/m^3 groups. During the 13-week studies, the H2000 chambers were used for the 0, 0.6, 2.5, and 10 mg/m^3 groups, and the H1000 chambers were used for the 1.2 and 5 mg/m^3 groups. In the 2-year studies, the H2000 chambers were used to expose the rats, and the H1000 chambers were used to expose the mice. The air flow rate in the 16-day studies corresponded to 12 $\pm$ 2 air changes per hour. In the 13-week studies, the air flow rate was 12 $\pm$ 2 ft^3/min in the H2000 chambers and 7 $\pm$ 1 ft^3/min in the H1000 chambers, corresponding to 3.86 to 21.32 (rats) and 10.06 to 19.44 (mice) air changes per hour. In the 2-year studies, the air flow rate was 14.6 $\pm$ 2.0 ft^3/min in the rat chambers and 8.7 $\pm$ 1.2 ft^3/min in the mouse chambers, corresponding to 15 $\pm$ 2 air changes per hour. To reduce the spatial variation of aerosol concentration and to increase the uniformity of mixing, the aerosol was diluted in a radial dilutor prior to introduction into the chamber, and a small boxer fan (Model WS 2107FL-1002, Newark Electronics, Chicago, IL) with a flow rate of 60 ft^3/min was placed below the aerosol entrance to further mix the aerosol as it entered the chamber. Animal cages were rotated weekly to reduce the variation of concentrations of aerosols that the animals were being exposed to during the 13-week and 2-year studies. Diagrams of the 13-week and 2-year exposure suites are shown in Figures K4 and K5, respectively.

AEROSOL CONCENTRATION MONITORING

In the 13-week and 2-year studies, the aerosol concentrations were determined gravimetrically from three 2-hour samples (3 L/min flow rate) from each exposure chamber during each 6-hour exposure day. The background concentrations of total suspended particles in the control chambers were monitored each exposure day of the 2-year studies by collecting one 6-hour filter sample; samples were collected overnight from the control chambers during the 16-day and 13-week studies. The mean concentration of total suspended particles in the control chamber was 0.08 mg particles/m^3 in the 16-day studies and was 0.07 mg particles/m^3 in the 13-week studies. In the 2-year studies, the mean concentrations of total suspended particles were 0.02 $\pm$ 0.01 mg particle/mg^3 in the rat control chamber and 0.01 $\pm$ 0.01 mg particle/m^3 in the mouse control chamber.

All samples in the 13-week and 2-year studies were collected after the initial 8 minutes (T_{90}) of aerosol generation at a flow rate of 3 L/min. The flow rate was monitored with orifice meters. To determine aerosol concentration, samples were collected with 25 mm fiberglass filters (Type AE, Gelman, Ann Arbor, MI) during the 13-week studies and with 25 mm, Teflon®-coated, fiberglass filters with a pore size

of 0.1 μm (Zefluor, Gelman, Ann Arbor, MI) during the 2-year studies. The quantity of nickel oxide collected on the filters was determined gravimetrically by weighing the filters with an electrobalance (Cahn 29, Cahn Instruments, Cerrito, CA) before and after the collection of the samples. The aerosol mass concentrations were calculated by dividing the mass increment (mg) by the volume sampled (m^3); the means and standard deviations of each chamber were calculated for each exposure day. Daily mean exposure concentrations for the 13-week studies are presented in Figures K6 and K7. Weekly mean exposure concentrations for the 2-year studies are presented in Figures K8 and K9.

A continuous aerosol monitor (Model RAM-S, GCA, Co., Bedford, MA) was used to monitor the stability of the aerosol concentrations and to determine the need to adjust the aerosol generation system during exposures. The RAM-S was used to monitor each chamber for at least 2 minutes at the beginning, middle, and end of each filter sampling period. The RAM-S unit has a self-contained sampling system which operates at 2 L/min.

Aerosol concentration was also quantitated with the RAM-S. The RAM-S voltage output was calibrated against the mass concentration obtained gravimetrically. The average of three RAM-S voltage readings taken during a filter-sampling period were plotted versus the aerosol concentration determined gravimetrically. Linear regression analysis was performed monthly on these data, and the RAM-S voltage readings (volts) were converted to mass concentration (mg/m^3) based on the slope and intercept of the regression line fitted to the data. The mean and standard deviation of the concentrations were calculated each exposure day for each chamber. The coefficient of variation from the RAM-S measurement was used as an indication of aerosol stability for each exposure day. RAM-S and filter samples were taken at the middle level of the H2000 and H1000 chambers above the animal cage. The probe for the filter sample was at the front of each chamber, and the probe for the RAM-S was at the back of each chamber.

CHAMBER ATMOSPHERE CHARACTERIZATION

Aerosol size distribution was determined once during the 16-day and 13-week studies and monthly during the 2-year studies for each exposure chamber with a Lovelace multijet cascade impactor operated at a flow rate of 15 L/min. The sampling period ranged from 30 minutes to 6 hours depending on the chamber concentration. Stainless steel shimstock coated with apiezon grease was used as impactor substrate. The amount of nickel oxide on each stage was determined by the difference in stage weight before and after the sample was collected. The mass medium aerodynamic diameter and the geometric standard deviation were calculated from the mass data, effective cutoff diameter of each stage, and impactor flow rate. The results are presented in Tables K1 through K4.

Prior to the start of the studies, the generated aerosol was sampled and compared to the bulk sample by atomic absorption and X-ray diffraction analyses. The nickel content of both samples was identical, and their diffraction patterns conformed to the standard pattern (# 22-1189) published by the Joint Committee on Powder Diffraction Standards. The data supports the conclusion that the generation system did not change the crystal structure of the bulk chemical.

Results of analyses of the nickel content of the aerosol during the 13-week studies indicated the nickel content to be 78.81% $\pm$ 5.46%, which is consistent with the theoretical value of 78.58% nickel. Nickel oxide aerosol filter samples were collected from the 0.62 and 2.5 mg/m^3 rat chambers during week 4 of exposure during the 2-year study and were analyzed for nickel content by atomic absorption spectroscopy to verify the stability of the aerosol. Chemical analysis of these filter samples indicated that the aerosols contained 72% and 70% nickel, respectively. These values are somewhat below the average percent nickel found in the bulk nickel oxide and are below the theoretical value. Since low values for nickel

were occasionally reported by Huffman Laboratories for bulk chemical analysis, these low values were not considered to be significant.

Uniformity of aerosol concentration in the exposure chambers was measured prior to the start of the studies without animals in the chambers and with animals during the first week of exposure, and was checked quarterly during the 2-year studies. Three samples were collected with the RAM-S at a specified reference point in each chamber at the start, middle, and end of the procedure. One sample each was collected for the other locations. The total variation of aerosol concentrations is the coefficient of variation of samples collected at different locations, and the temporal variation is the coefficient of variation of the three reference samples. In the 13-week studies, the temporal variations ranged from 1% to 17%, and the spatial variations ranged from 0% to 3%. For rats in the 2-year studies, the mean temporal variations of aerosol concentration during exposure were between 1.46% and 2.76%, and the mean spatial variations were between 2.50% and 8.45%. For mice in the 2-year studies, the mean temporal variations were between 1.39% and 2.25%, and the mean spatial variations were between 3.78% and 4.89%.

The aerosol rise and fall time (T_{90}) was determined with a RAM-S, and an exposure day was set at 6 hours plus T_{90}. A T_{90} of 8 minutes was used during all studies.

Residual concentration of nickel oxide in the chambers during nonexposure hours was evaluated gravimetrically once during the 16-day studies, once during the 13-week studies, and once during the first 2 weeks of exposure and quarterly thereafter during the 2-year studies. The filter samples were collected overnight (about 15 hours) at a flow rate of 3 L/min. Samples were collected from the 30 mg/m^3 chamber during the 16-day studies and from the 10 mg/m^3 chamber during the 13-week studies. During the 2-year studies, samples were collected from the 2.5 mg/m^3 rat chamber and from the 5 mg/m^3 mouse chamber. If the weight of the material collected on the filter was greater than 200 μg, the material collected was analyzed for nickel content by atomic absorption spectroscopy. The mass of the particles collected on the filter during the 16-day and 13-week studies never exceeded 200 μg. The mass of the particles collected exceeded 200 μg four times during the 2-year rat study and three times during the 2-year mouse study, and these samples were analyzed for nickel content. Results of chemical analysis of these filter samples by atomic absorption spectroscopy indicated that the aerosol collected on the filter consisted chiefly of non-nickel-containing material.

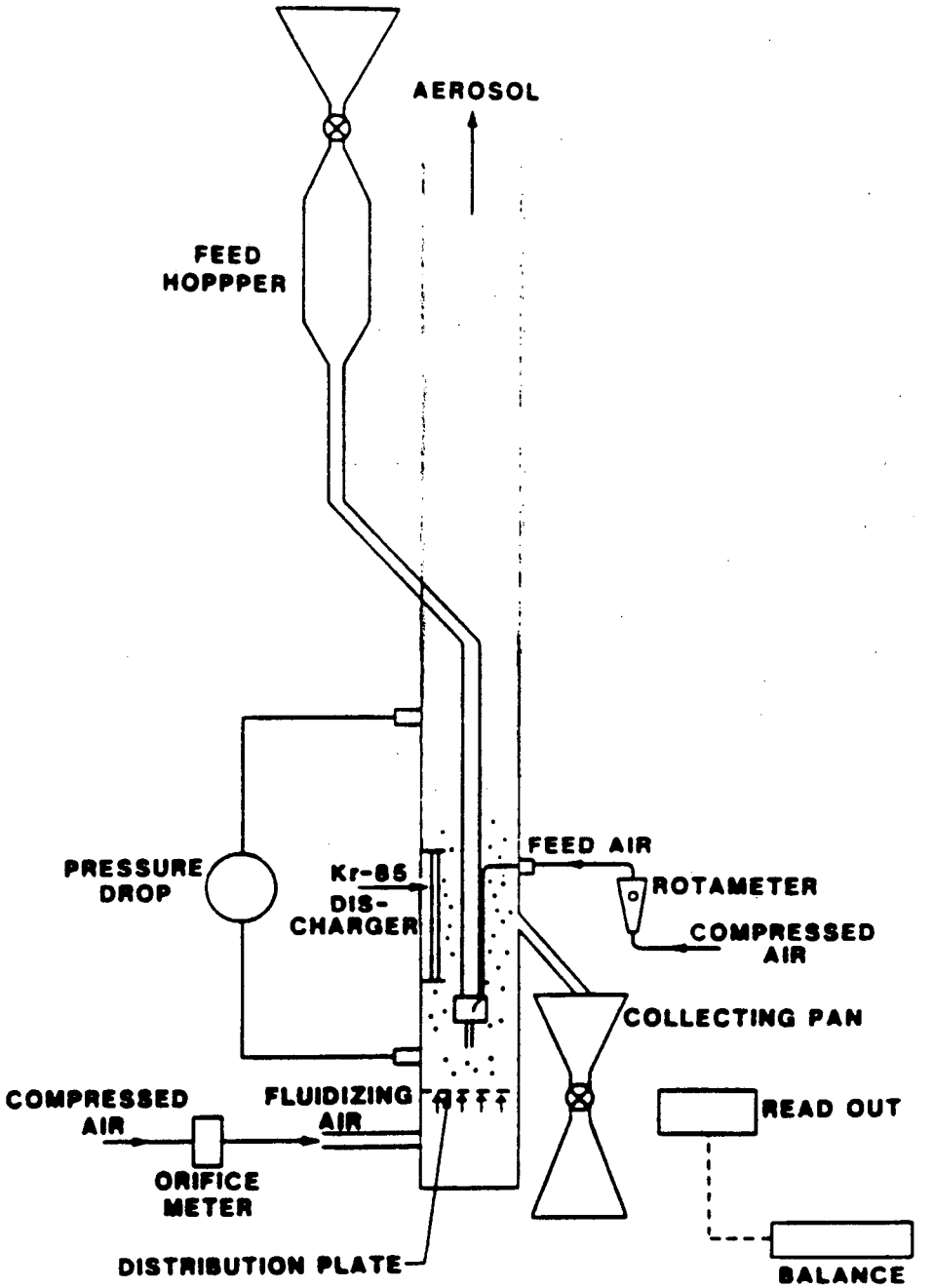

FIGURE K1
Schematic of the Generation System

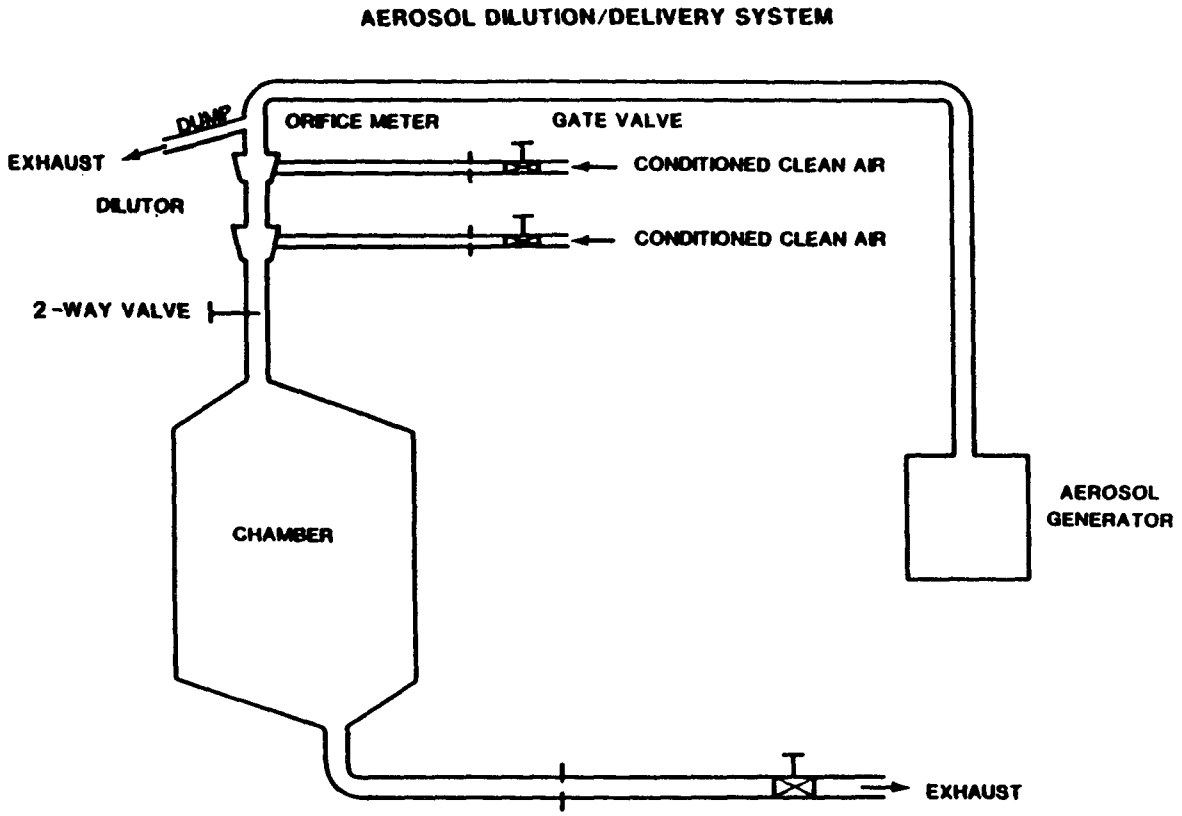

FIGURE K2
Schematic of the Nickel Oxide Aerosol Delivery System

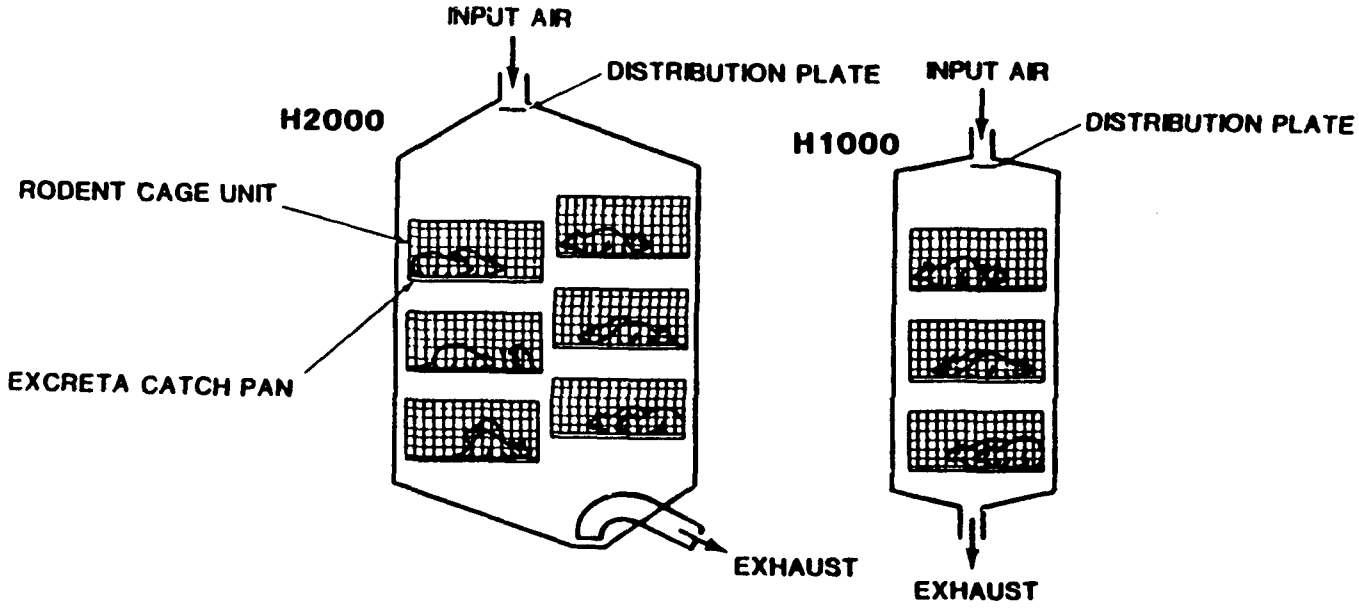

FIGURE K3
Schematic of the H1000 and H2000 Exposure Chambers

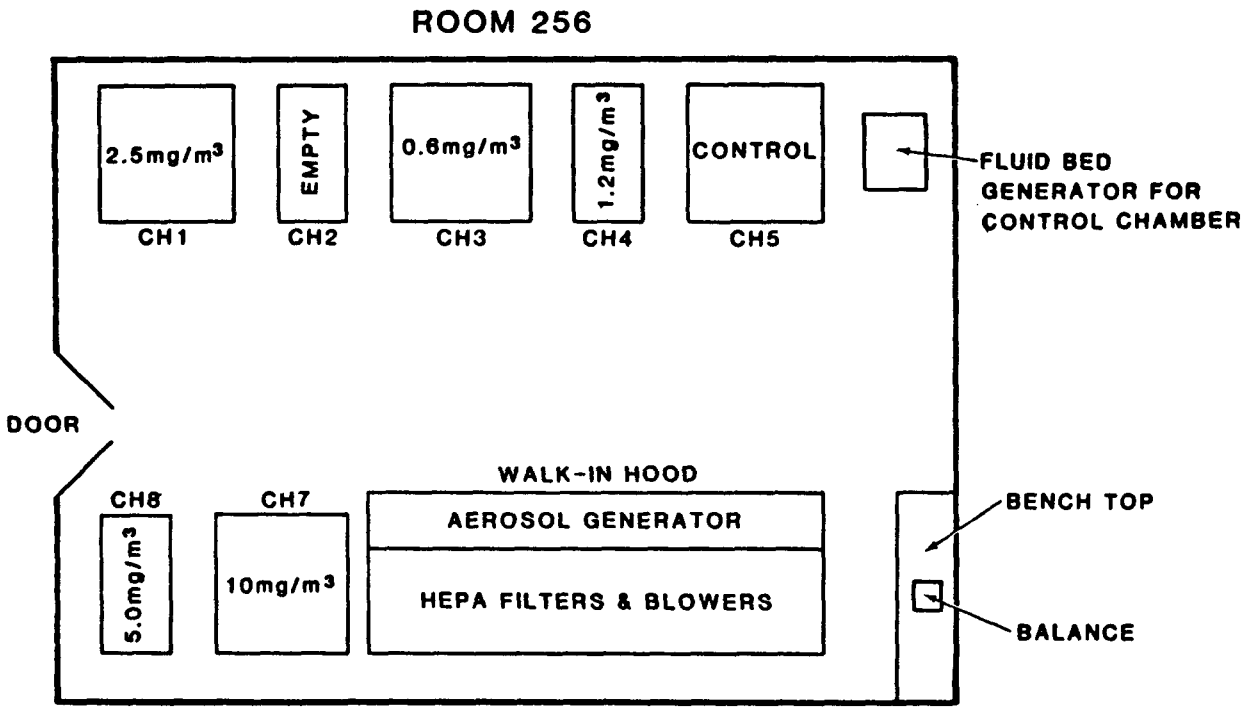

FIGURE K4
13-Week Nickel Oxide Inhalation Suite

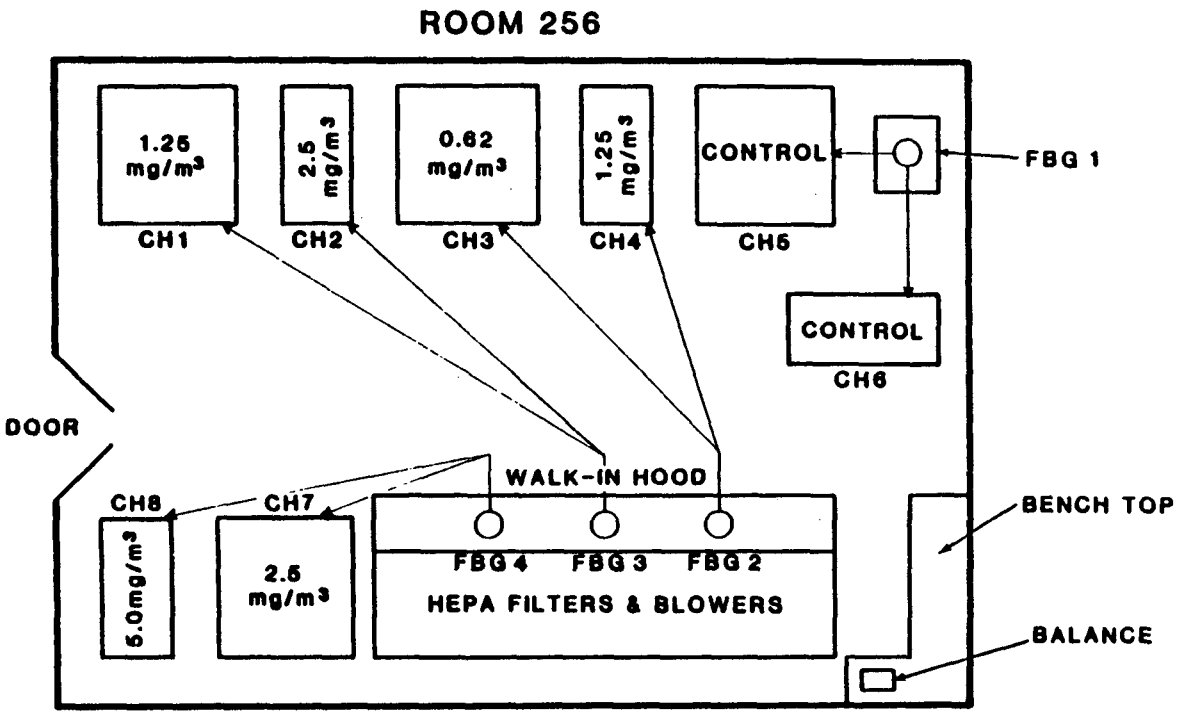

FIGURE K5
2-Year Nickel Oxide Inhalation Suite

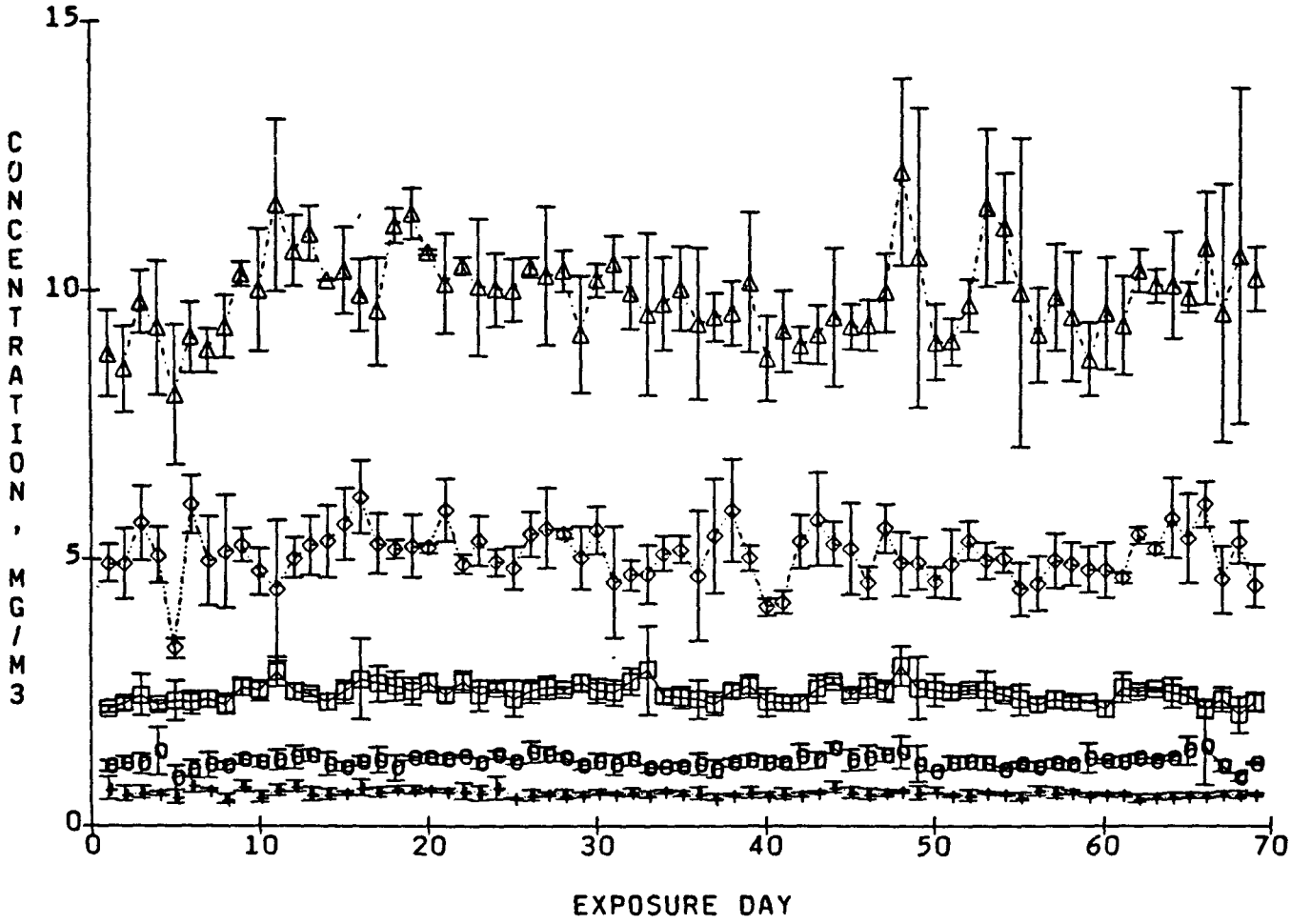

FIGURE K6
Daily Mean Filter Concentrations and Standard Deviations in the 13-Week Inhalation Study in Rats

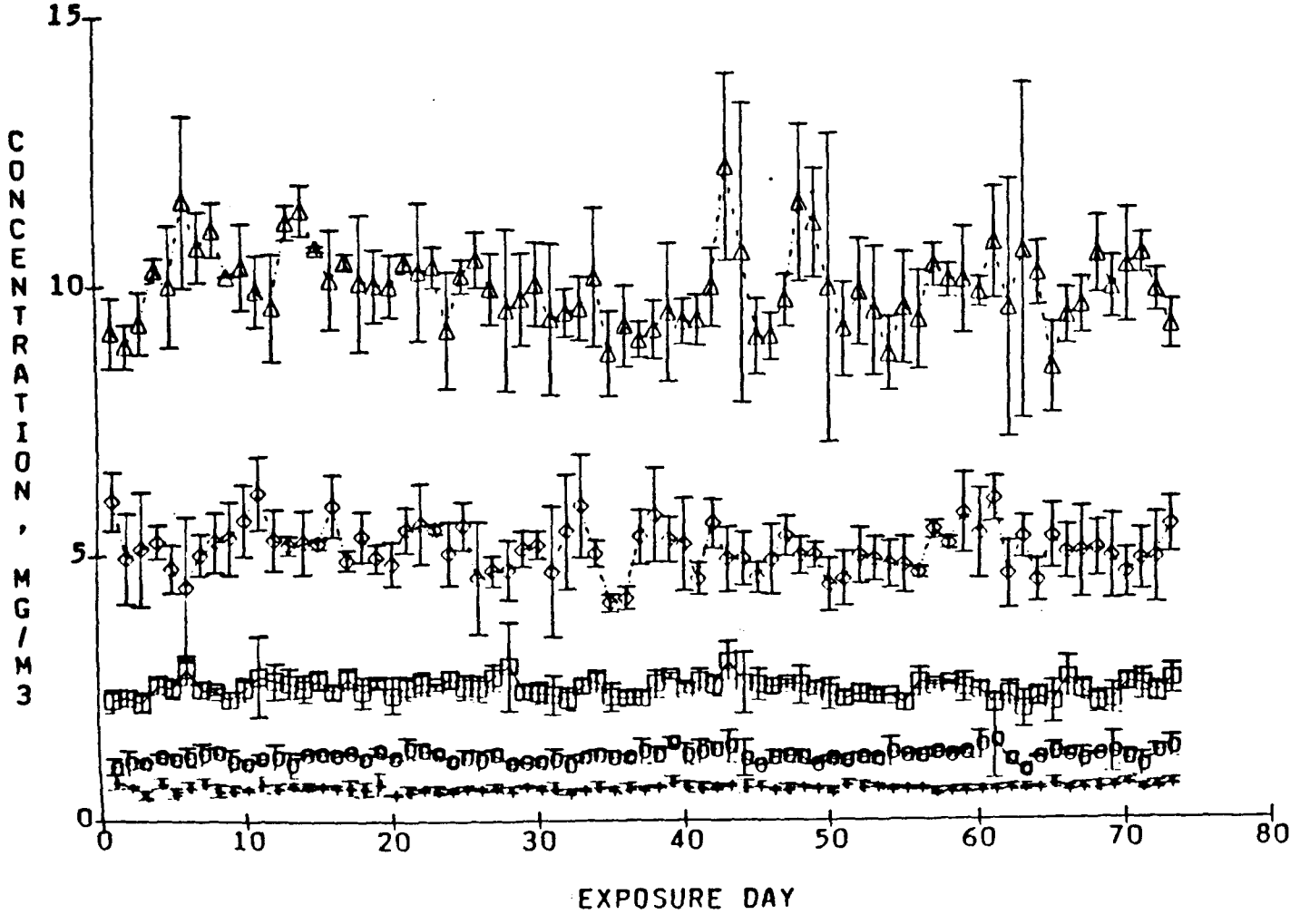

FIGURE K7
Daily Mean Filter Concentrations and Standard Deviations in the 13-Week Inhalation Study in Mice

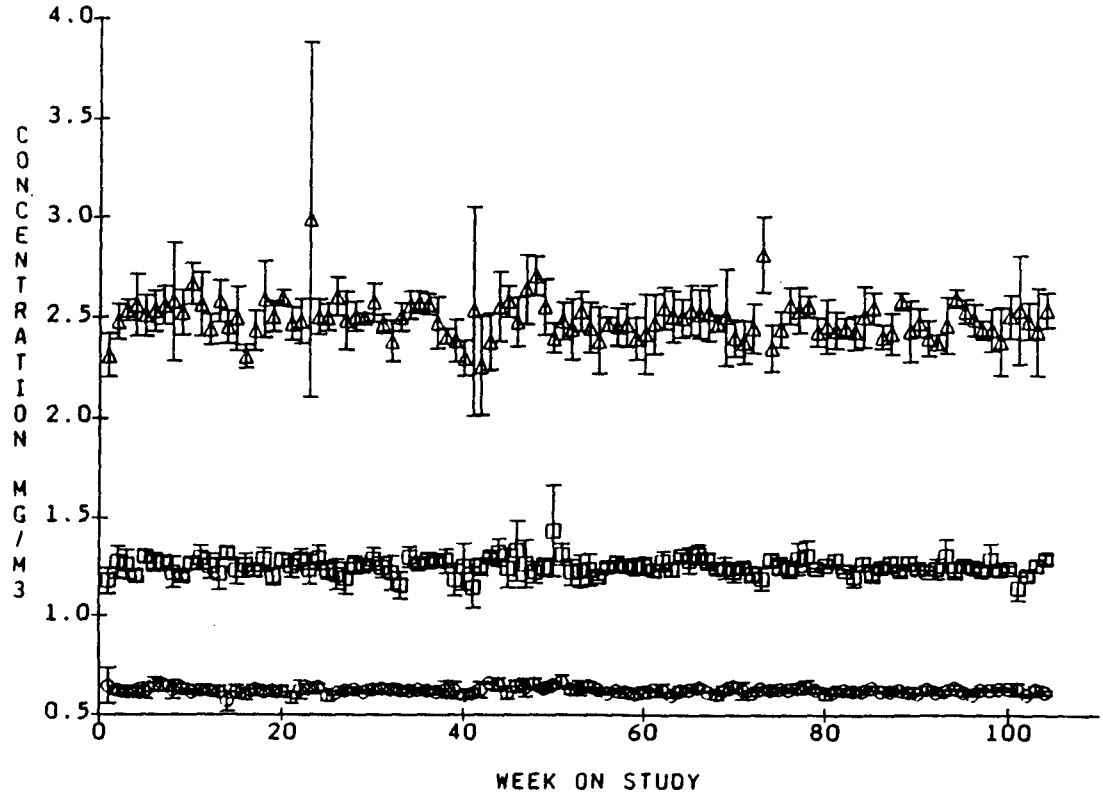

FIGURE K8
Weekly Mean Filter Concentrations and Standard Deviations in the 2-Year Inhalation Study in Rats

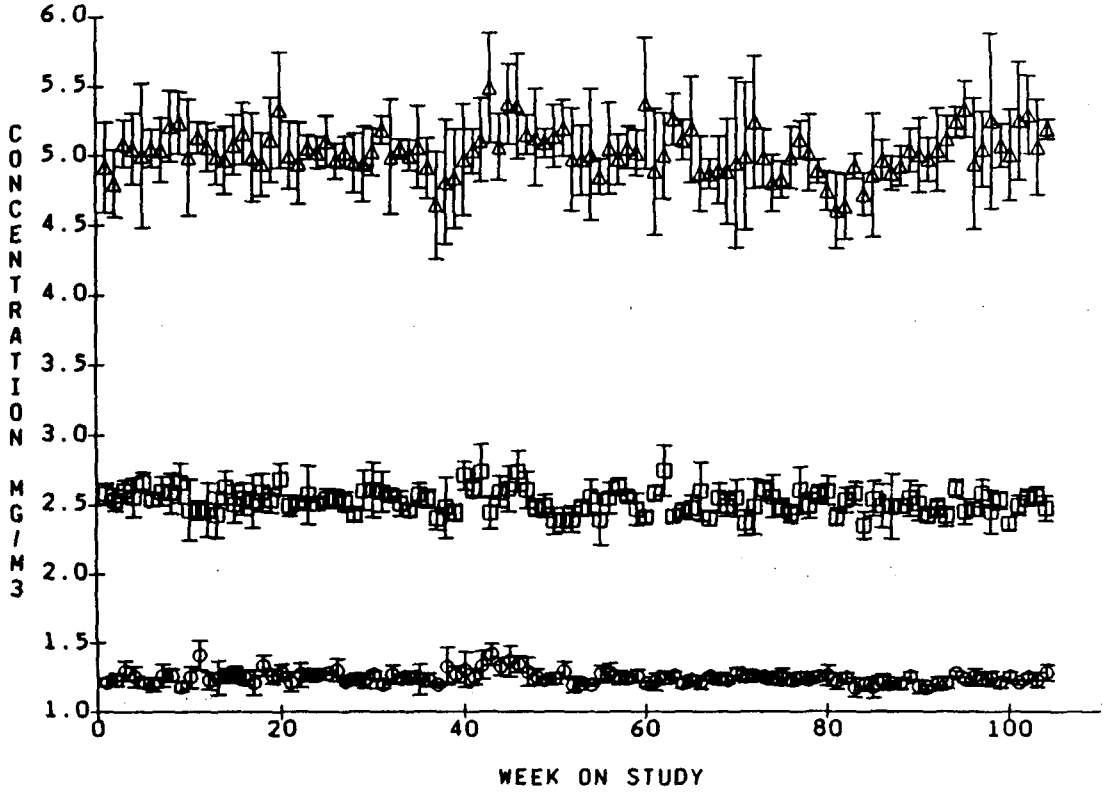

FIGURE K9
Weekly Mean Filter Concentrations and Standard Deviations in the 2-Year Inhalation Study in Mice

TABLE K1
Summary of Aerosol Size Measurements for the Rat and Mouse Chambers in the 16-Day Inhalation Studies of Nickel Oxide

Target Concentration (mg/m^3)	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation
1.2	2.81	1.81
2.5	3.21	1.82
5	2.89	2.13
10	2.56	1.88
30	3.29	2.04

TABLE K2
Summary of Aerosol Size Measurements for the Rat and Mouse Chambers in the 13-Week Inhalation Studies of Nickel Oxide

Target Concentration (mg/m^3)	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation
0.6	3.04	1.9
1.2	3.06	2.0
2.5	2.57	1.8
5	2.77	1.9
10	2.71	1.6

TABLE K3
Summary of Aerosol Size Measurements for the 0.62, 1.25, and 2.5 mg/m³ Rat Chambers in the 2-Year Inhalation Study of Nickel Oxide

Date	0.62 mg/m³		1.25 mg/m³		2.5 mg/m³	
	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation
April 1988	2.47	1.85	2.49	1.59	2.37	1.86
May 1988	2.35	1.96	2.33	1.92	2.58	1.87
June 1988	2.26	2.05	2.46	1.71	2.29	1.78
July 1988	2.21	2.05	2.42	1.76	2.13	1.71
August 1988	2.09	1.98	1.99	1.76	2.19	1.61
September 1988	2.10	2.02	2.06	1.70	2.06	1.60
October 1988	2.38	1.77	2.20	1.66	2.31	1.58
November 1988	2.48	1.98	2.26	1.71	2.07	1.75
December 1988	2.15	1.88	2.13	1.84	2.16	1.58
January 1989	2.28	2.08	2.58	3.51	2.33	1.82
February 1989	2.14	2.05	1.95	1.92	2.27	1.76
March 1989	2.10	1.97	2.13	1.82	2.25	1.76
April 1989	2.46	1.95	2.15	1.95	2.29	1.76
May 1989	2.19	1.86	2.22	1.90	2.21	1.97
June 1989	2.18	1.91	2.31	1.94	2.39	1.81
July 1989	2.01	1.92	2.21	1.86	2.35	1.94
August 1989	1.99	1.92	2.01	1.96	2.23	1.88
September 1989	2.11	2.03	2.10	1.82	2.03	1.82
October 1989	2.22	1.99	2.36	1.88	2.16	1.90
November 1989	2.27	2.08	2.29	1.83	2.27	1.84
December 1989	2.34	1.98	2.29	1.88	2.19	1.84
January 1990	2.17	1.92	2.14	1.78	1.89	1.83
February 1990	2.11	2.05	2.35	1.81	1.94	1.97
March 1990	2.08	1.93	2.07	1.73	1.97	1.86
Mean ± standard deviation	2.21 ± 0.14	1.97 ± 0.08	2.23 ± 0.17	1.89 ± 0.36	2.21 ± 0.16	1.80 ± 0.11

TABLE K4
Summary of Aerosol Size Measurements for the 1.25, 2.5, and 5 mg/m³ Mouse Chambers in the 2-Year Inhalation Study of Nickel Oxide

	1.25 mg/m³		2.5 mg/m³		5 mg/m³	
Date	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation	Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation
May 1988	2.82	1.90	2.52	1.93	2.87	1.82
June 1988	2.83	1.81	2.65	1.82	2.68	1.79
July 1988	2.44	1.92	2.41	1.87	2.77	1.85
August 1988	2.80	1.73	2.32	1.84	2.31	1.55
September 1988	2.31	1.74	2.34	1.74	2.50	1.59
October 1988	2.99	1.65	2.70	1.63	2.70	1.66
November 1988	2.40	1.85	2.46	1.69	2.48	1.64
December 1988	2.22	1.80	2.55	1.91	2.55	1.64
January 1989	2.46	1.90	2.40	1.86	2.65	1.59
February 1989	2.57	2.00	2.33	1.87	2.46	1.82
March 1989	2.30	1.88	2.32	1.73	2.60	1.80
April 1989	2.62	1.91	2.32	1.78	2.77	1.83
May 1989	2.56	1.86	2.43	1.85	2.60	1.76
June 1989	2.22	1.92	2.48	1.84	2.67	1.91
July 1989	2.21	2.00	2.15	1.84	2.52	1.80
August 1989	2.30	1.96	2.46	1.74	2.58	1.83
September 1989	2.32	1.85	2.34	1.79	2.49	1.72
October 1989	2.67	1.87	2.49	1.73	2.48	1.80
November 1989	2.40	1.78	2.50	1.81	2.72	1.74
December 1989	2.41	1.88	2.61	1.75	2.45	1.85
January 1990	2.21	1.75	2.34	1.88	2.22	1.78
February 1990	2.32	1.90	2.37	1.77	2.37	1.89
March 1990	2.35	2.04	2.30	1.73	2.28	1.69
April 1990	2.36	1.86	2.28	1.97	2.49	1.85
Mean ± standard deviation	2.46 ± 0.22	1.87 ± 0.09	2.42 ± 0.13	1.81 ± 0.08	2.55 ± 0.16	1.76 ± 0.10

APPENDIX L
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-07 RAT AND MOUSE RATION

TABLE L1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

[a] NCI, 1976; NIH, 1978
[b] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE L2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

[a] Per ton (2,000 lb) of finished product

TABLE L3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.9 ± 0.80	21.70 — 24.20	25
Crude fat (% by weight)	5.40 ± 0.30	4.60 — 5.90	25
Crude fiber (% by weight)	3.60 ± 0.40	2.80 — 4.30	25
Ash (% by weight)	6.60 ± 0.30	6.10 — 7.30	25
Amino Acids (% of total diet)			
Arginine	1.287 ± 0.084	1.100 — 1.390	10
Cystine	0.306 ± 0.075	0.181 — 0.400	10
Glycine	1.160 ± 0.050	1.060 — 1.220	10
Histidine	0.580 ± 0.024	0.531 — 0.608	10
Isoleucine	0.917 ± 0.034	0.867 — 0.965	10
Leucine	1.972 ± 0.052	1.850 — 2.040	10
Lysine	1.273 ± 0.051	1.200 — 1.370	10
Methionine	0.437 ± 0.115	0.306 — 0.699	10
Phenylalanine	0.994 ± 0.125	0.665 — 1.110	10
Threonine	0.896 ± 0.055	0.824 — 0.985	10
Tryptophan	0.223 ± 0.160	0.107 — 0.671	10
Tyrosine	0.677 ± 0.105	0.564 — 0.794	10
Valine	1.089 ± 0.057	0.962 — 1.170	10
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.233	1.830 — 2.570	9
Linolenic	0.277 ± 0.036	0.210 — 0.320	9
Vitamins			
Vitamin A (IU/kg)	65,230 ± 1,933	4,180 — 12,140	25
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 — 6,300	4
α-Tocopherol (ppm)	36.92 ± 9.32	22.5 — 48.9	9
Thiamine (ppm)	18.90 ± 2.40	16.0 — 28.0	25
Riboflavin (ppm)	7.92 ± 0.93	6.10 — 9.00	10
Niacin (ppm)	100.95 ± 25.92	65.0 — 150.0	9
Pantothenic acid (ppm)	30.30 ± 3.60	23.0 — 34.6	10
Pyridoxine (ppm)	9.25 ± 2.62	5.60 — 14.0	10
Folic acid (ppm)	2.51 ± 0.64	1.80 — 3.70	10
Biotin (ppm)	0.267 ± 0.049	0.19 — 0.35	10
Vitamin B_{12} (ppb)	40.14 ± 20.04	10.6 — 65.0	10
Choline (ppm)	3,068 ± 314	2,400 — 3,430	9
Minerals			
Calcium (%)	1.25 ± 0.10	1.00 — 1.50	25
Phosphorus (%)	0.95 ± 0.03	0.90 — 1.00	25
Potassium (%)	0.887 ± 0.067	0.772 — 0.971	8
Chloride (%)	0.526 ± 0.092	0.380 — 0.635	8
Sodium (%)	0.315 ± 0.034	0.258 — 0.370	10
Magnesium (%)	0.168 ± 0.008	0.151 — 0.180	10
Sulfur (%)	0.274 ± 0.063	0.208 — 0.420	10
Iron (ppm)	356.2 ± 90.0	255.0 — 523.0	10
Manganese (ppm)	92.24 ± 5.35	81.7 — 99.4	10
Zinc (ppm)	58.14 ± 9.91	46.1 — 81.6	10
Copper (ppm)	11.50 ± 2.40	8.090 — 15.39	10
Iodine (ppm)	3.70 ± 1.14	1.52 — 5.83	10
Chromium (ppm)	1.71 ± 0.45	0.85 — 2.09	9
Cobalt (ppm)	0.797 ± 0.23	0.490 — 1.15	6

TABLE L4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.22 ± 0.17	0.05 — 0.60	25
Cadmium (ppm)	0.09 ± 0.02	0.05 — 0.10	25
Lead (ppm)	0.25 ± 0.18	0.10 — 1.00	25
Mercury (ppm)	0.05 ± 0.02	0.02 — 0.11	25
Selenium (ppm)	0.42 ± 0.25	0.16 — 1.21	25
Aflatoxins (ppb)[c]	<5.0		24
Nitrate nitrogen (ppm)[d]	15.90 ± 8.00	2.60 — 24.0	25
Nitrite nitrogen (ppm)[d]	0.19 ± 0.15	<0.10 — 0.60	25
BHA (ppm)[e]	1.52 ± 0.58	0.10 — 2.00	25
BHT (ppm)[e]	1.28 ± 0.61	0.10 — 3.00	25
Aerobic plate count (CFU/g)[e]	64,828 ± 72,281	6,700 — 320,000	25
Coliform (MPN/g)[f]	48 ± 219	3 — 11,200	25
Escherichia coli (MPN/g)[f]	<3		25
Salmonella (MPN/g)[f]	Negative		25
Total nitrosoamines (ppb)	8.40 ± 3.30	3.60 — 16.50	25
N-Nitrosodimethylamine (ppb)	6.20 ± 2.90	2.60 — 13.00	25
N-Nitrosopyrrolidine (ppb)	2.15 ± 1.25	0.90 — 5.20	25
Pesticides (ppm)			
α-BHC[h]	<0.01		25
β-BHC	<0.02		25
γ-BHC	<0.01		25
δ-BHC	<0.01		25
Heptachlor	<0.01		25
Aldrin	<0.01		25
Heptachlor epoxide	<0.01		25
DDE	<0.01		25
DDD	<0.01		25
DDT	<0.01		25
HCB	<0.01		25
Mirex	<0.01		25
Methoxychlor	<0.05		25
Dieldrin	<0.01		25
Endrin	<0.01		25
Telodrin	<0.01		25
Chlordane	<0.05		25
Toxaphene	<0.1		25
Estimated PCBs	<0.2		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.1		25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion	0.24 ± 0.23	<0.05 — 1.00	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

[a] CFU = colony forming units, MPN = most probable number, BHC is hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] No aflatoxin measurement was recorded for the lot milled on 2 October 1989.
[d] Sources of contamination: alfalfa, grains, and fish meal
[e] Sources of contamination: soy oil and fish meal
[f] All values were corrected for percent recovery.

APPENDIX M
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from randomly selected rats and mice during the 13-week and 2-year studies. Blood from each animal was collected, allowed to clot and the serum separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
13-Week Study	
ELISA	
PVM (pneumonia virus of mice)	Study termination
RCV (rat coronavirus)	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
2-Year Study	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM	7 and 15 months, study termination
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	7 and 15 months, study termination
Sendai	7 and 15 months, study termination
Hemagglutination Inhibition	
H-1	7 and 15 months, study termination
KRV	7 and 15 months, study termination

MICE

13-Week Study

ELISA	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
Mouse adenoma virus	Study termination
MHV (mouse hepatitis virus)	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
Hemagglutination Inhibition	
K (papovavirus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination

2-Year Study

ELISA	
Ectromelia virus	7 and 15 months, study termination
GDVII	7 and 15 months, study termination
LCM	15 months, study termination
MVM	7 and 15 months, study termination
Mouse adenoma virus	7 and 15 months, study termination
MHV	7 and 15 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	7 and 15 months, study termination
Reovirus 3	7 and 15 months, study termination
Sendai	7 and 15 months, study termination
Immunofluorescence Assay	
EDIM	7 and 15 months, study termination
LCM	7 months
MVM	Study termination
Hemagglutination Inhibition	
K	7 and 15 months, study termination
MVM	Study termination
Polyoma virus	7 and 15 months, study termination

RESULTS

For the 13-week inhalation studies with rats and mice, all serology test results were negative. Three rats had positive titers to *M. arthritidis* at the end of the 2-year study.

Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only sporadic samples were positive, and there were no clinical signs or histopathologic changes of *M. arthritidis* infection in animals with positive titers. Accordingly, *M. arthritidis*-positive titers were considered to be false positive.

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